

MICROBIOME

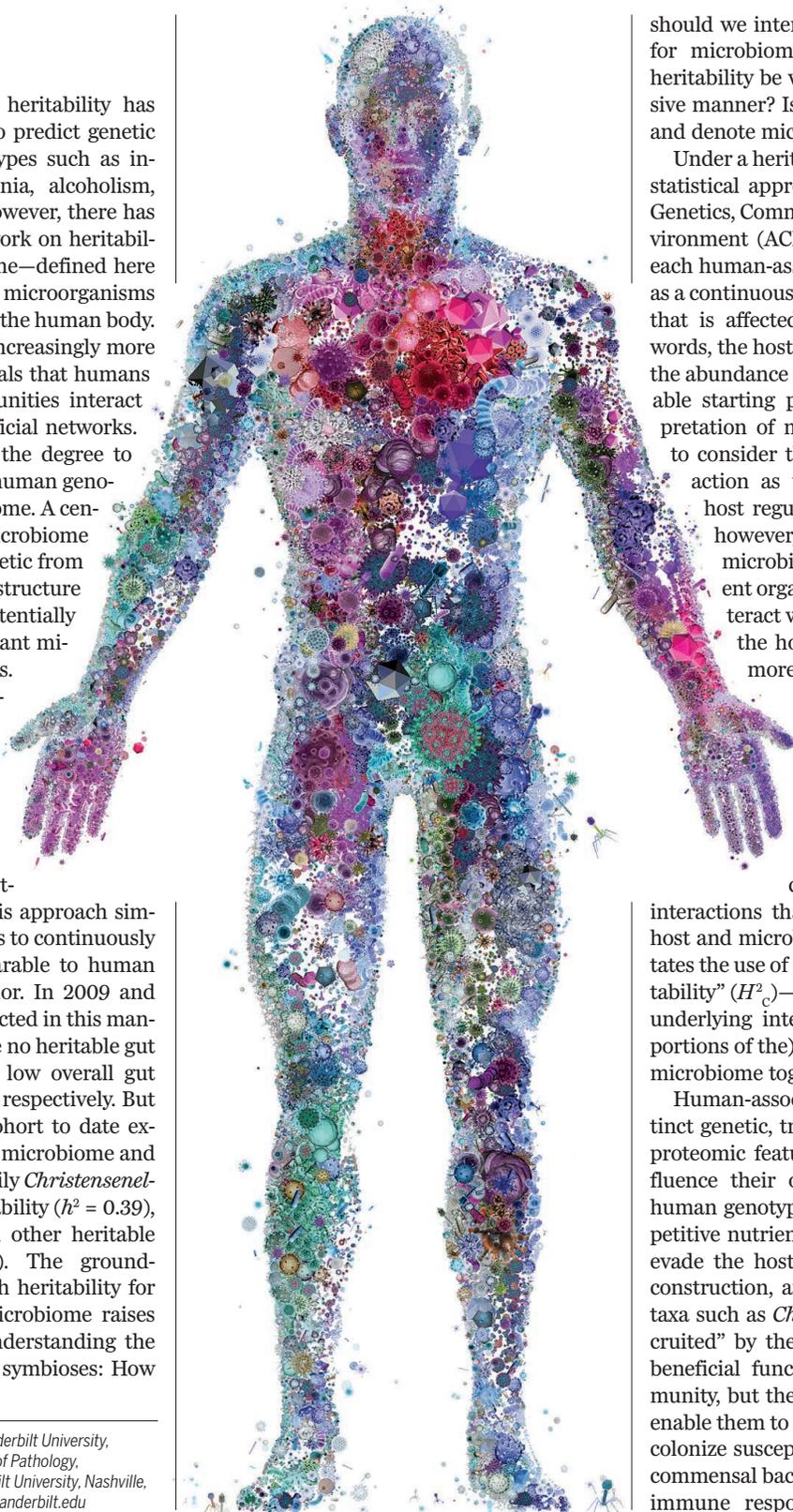
Rethinking heritability of the microbiome

How should microbiome heritability be measured and interpreted?

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For almost a century, heritability has been routinely used to predict genetic influences on phenotypes such as intelligence, schizophrenia, alcoholism, and depression (1). However, there has been relatively little work on heritability of the human microbiome—defined here as the number and types of microorganisms and viruses present in or on the human body. This question has become increasingly more interesting as research reveals that humans and their microbial communities interact in complex and often beneficial networks. An underlying question is the degree to which environment versus human genotype influences the microbiome. A central goal of quantifying microbiome heritability is to discern genetic from environmental factors that structure the microbiome and to potentially identify functionally important microbial community members.

Twin-based studies provide one method for quantifying heritability (h^2) of microbial taxa. In such analyses, heritability is measured by comparing variation in microbial taxon abundances that is attributable to human genetics. This approach simplifies microbial abundances to continuously varying phenotypes, comparable to human height, weight, and eye color. In 2009 and 2012, studies of twins conducted in this manner concluded that there are no heritable gut microbial members (2), or low overall gut microbiome heritability (3), respectively. But in 2014, the largest twin cohort to date examined members of the gut microbiome and found that the bacterial family *Christensenellaceae* has the highest heritability ($h^2 = 0.39$), and associates closely with other heritable gut bacterial families (4). The groundbreaking discovery of a high heritability for members of the human microbiome raises specific questions about understanding the genetics of human-microbe symbioses: How



should we interpret what heritability means for microbiome studies? Can microbiome heritability be viewed in a more comprehensive manner? Is h^2 the only term to measure and denote microbiome heritability?

Under a heritability analysis with standard statistical approaches [such as the Additive Genetics, Common Environment, Unique Environment (ACE) model], the abundance of each human-associated microbe is presented as a continuously varying, quantitative “trait” that is affected by host genetics—in other words, the host genome significantly dictates the abundance of a microbe. Although a suitable starting point, this host-centric interpretation of microbiome heritability tends

to consider the human-microbiome interaction as unidirectional, in which the host regulates colonization. This view, however, is only half of the story. The microbiome is a collection of different organisms with genotypes that interact with each other as well as with the host to achieve colonization. A more comprehensive view is advisable

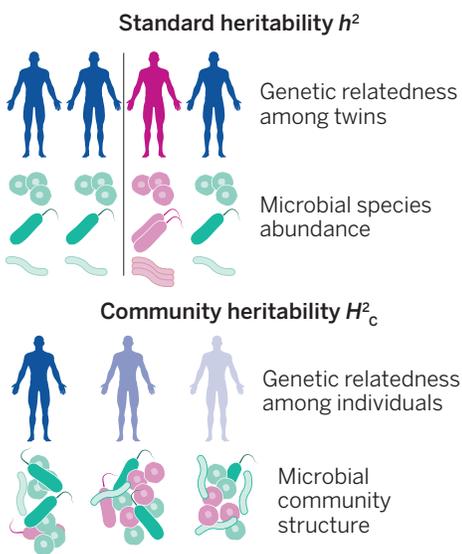
in which both the host and the microbiome play a role in heritability. This view, based on community genetics principles, requires that studies adopt a conceptual foundation of interspecies (genotype-by-genotype)

interactions that drive the assembly of the host and microbial consortia. It also necessitates the use of a measure—“community heritability” (H^2)—that reflects genetic variation underlying interactions with the entire (or portions of the) community—in this case, the microbiome together with its human host.

Human-associated microbes contain distinct genetic, transcriptomic, metabolic, and proteomic features that can reciprocally influence their own colonization of specific human genotypes. These features span competitive nutrient acquisition, mechanisms to evade the host immune system, and niche construction, among others. Thus, heritable taxa such as *Christensenellaceae* may be “recruited” by the human genome to perform beneficial functions in the microbial community, but they also may encode traits that enable them to circumvent host defenses and colonize susceptible genotypes. For example, commensal bacteria tolerate or evade human immune responses by modifying surface

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components in their cell walls and outer membranes (5). Other microbes proactively subvert the immune system by injecting effector proteins into host immune cells to kill them (6). Microbes may alter the expression of genes involved in regulating immune, developmental, and metabolic functions (7–10). Communities of microbes can also alter their human environment by forming internal biofilms. Biofilms can provide protection against the host immune response, afford stability in fluctuating environments, and promote the survival of a microbial community (11). Put simply, microbiome heritability can represent three outcomes: host control of the microbiome, host susceptibility to the microbiome, or a combination of host control and susceptibility. Interspecies interactions (host-microbe and microbe-microbe) thus underlie the emergent property of microbiome heritability.



Analyzing heritability. Under standard heritability (h^2) analysis, each microbe is a quantitative “trait” that is encoded by host genetics. Comparing monozygotic versus dizygotic twins allows an indirect estimate of the additive genetic factors affecting that microbe’s abundance. Community heritability (H^2_c) emphasizes that the host is part of the ecosystem and measures the extent to which whole community phenotype variation is due to genetic variation in the host. It specifies that host genetic variation will have predictable effects on microbial community assembly.

Human-microbiome interactions tend to be viewed through the lens of host regulation. A key point when discussing community-wide symbiotic interactions is that heritability denotes host involvement rather than control of microbiome assembly. Thus, human genetic effects on the microbiome are most easily understood as genotype-by-genotype (i.e., hologenomic) interactions between the host and other microbial members (12). Without knowing the mechanisms underlying

ing the heritability of a certain microbial member, we must be cautious in interpreting whether a highly heritable microbe in any symbiosis is harmful, harmless, or beneficial to the whole system.

In addition to taking a comprehensive view of microbiome heritability, it is important to understand the ecological genetics principle of broad-sense community heritability (H^2_c) (13). H^2_c emphasizes that the host is part of an ecosystem and measures the extent to which variation in “whole-community” phenotype is due to genetic variation in the foundation (i.e., host) species of the community. It therefore specifies that host genetic variation will have predictable effects on microbial community assembly (14), in addition to having effects on specific members of the microbiome, as measured by h^2 .

The whole-community phenotype is measured by ordination methods that cluster microbial community data into single scores used to compare compositional differences (i.e., β diversity) between the communities of various hosts. One such data clustering method is nonmetric multidimensional scaling (NMDS). Analysis of NMDS scores (by ANOVA, which tests whether there is significant variation in means among groups, among subgroups, within groups, etc.), would then identify the fraction of total variation in whole community phenotype that relates to genetic variation in the host (14).

The utility of this approach in addition to conventional heritability measurements is that it incorporates the vast interspecies interactions that contribute to a whole community phenotype, instead of considering individual microbial members as phenotypic extensions of the host. If these interactions have a heritable component (H^2_c), then the assembly of the community is nonrandom (i.e., via ecological selection). For host-microbiome symbioses, this has been referred to as “phylosymbiosis” (15). Given a significant H^2_c selection as an evolutionary force can potentially act on the community.

Presently, community heritability measurements have only been applied to ecological systems analyzing plant genetic influences on soil microbe, arthropod, bird, and mammal community structures (14). Human microbiome studies could adopt H^2_c to determine whether human genetic variation across the whole genome, or certain functional categories of genes, affects microbial community assembly. Twin-based microbiome studies could derive a NMDS score for the whole microbial community or from specific taxonomic levels to test if there is a significant association with human genetic relatedness across the cohort of twins. Further, transcriptomes, metabolomes, and proteomes could potentiate identification

of the candidate genes that affect microbiome heritability. Data integration from large “omics” data sets holds the potential to move the community genetics view of host and microbes from unspecified genetic effects on interacting species to precise gene-by-gene interactions.

The products of host genes work in intimate association with the products of microbial genes to enable functioning of the whole holobiont (14). Strong degrees of microbiome heritability could therefore have profound consequences for the ecology and evolution of human and all animal and plant holobionts. A crucial outcome of this community heritability view is to underscore the deterministic and predictable interactions between hosts and microbes. Further studies also need to consider the relative roles of vertical and horizontal transmission of microbial communities in heritability assessments. Thus, genetic analysis of whole community organization is an important frontier in the life sciences, particularly for fusing the fields of ecology and evolution and the taxonomic disciplines of zoology and botany with microbiology. The repurposing of community heritability from traditional macroecological systems (i.e., gardens) to microecological systems (i.e., human gut) will provide a more comprehensive view to studies of microbiome heritability. This view looks onwards, beyond the phenotype, to examine links at higher interspecies levels and holds the potential to unify community ecology and evolution concepts. In the words of the microbiologist Carl Woese: “Biologists now need to reformulate their view of evolution to study it in complex dynamic-systems terms.” ■

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