Our genes, our microbes

In recent years, large-scale genomic studies have been performed in attempts to determine how genetic variation in the human host influences the gut microbiome. As microbiome traits are very heterogeneous, new analytical approaches are needed to move this field forward. By using genetic tools, there is a huge opportunity to enrich our understanding of the complex link between humans and our intimately associated microbial species.

The microbiome has been implicated in many health-related traits, and is thought to affect many conditions, from neurological conditions to cancer. The close relationship between humans and their potentially trillions of microbial cells is a fascinating example of symbiosis. When this relationship is disturbed, there can be consequences on metabolism, disease and drug response. Understanding the interplay between humans and the microbiome is therefore an important facet to understanding overall health.

In 2016, *Nature Genetics* published a trio of papers that took a genome-wide association approach to analyze how human host genetics may affect the gut microbiome[1–3]. Although a lot of effort went into normalizing data collection as much as possible, there was little overlap in the reported findings. Many questions remained about the optimal choice for analysis method, sample processing, sequencing approach, phenotype analyzed and statistical thresholds. In addition, replication (or even finding appropriate cohorts for this) remained challenging. Still, the authors did identify associations between human genetic variants and microbiome composition (in the form of diversity or abundance).

Later, a 2018 study in *Nature*[4] reported that environment factors such as diet or drug treatment are much more influential in shaping the human gut microbiome than host genetics. Where does that leave the human genetics field? Are these microbiome genome-wide association studies (mbGWAS) still worthy endeavors?

We think that the field of human complex trait genetics has plenty of tools that are appropriate for analyzing the relationship between host genetics and the microbiome. Applying genetic techniques, such as Mendelian randomization approaches, is one way to try to extract more useful, causal information about the interactionsy between human host genetics, microbiome composition and various outcomes.

A major challenge in microbiome studies is untethering causality from correlation. Bacterial traits are highly related, and identification of causal effects of these traits on health or disease or even biomarker outcomes is not trivial. Steps have been made in this direction through the harnessing of Mendelian randomization[5] to begin to find causal relationships. The complex interactions between host genes, microbial genes, metabolites and disease are only beginning to be teased apart.

In 2021, the publication of larger mbGWAS using meta-analysis approaches[6,7] still only identified a few loci significantly associated with microbial traits. Although these studies provided valuable data and allow for interesting comparisons, they indicated that further studies would need new approaches to increase the discovery of new associations, and even more innovations to understand the biological meanings that underlie these associations.

Now, in a Perspective article in this issue of *Nature Genetics*, Sanna and colleagues[8] discuss the state of the microbiome GWAS field and present recommendations for areas that are poised for developments. Accompanying this article are two research studies[9,10] that use large cohorts with host genotyping and detailed phenotyping along with whole-genome metagenomic sequencing to identify further loci that are associated with microbial traits. These studies were able to robustly replicate associations at the *LCT* locus and the *ABO* locus, lending confidence to findings from earlier reports, now confirmed several times across different cohorts and different analyses. Many candidate loci for further exploration are also described.

In the Perspective[8], the authors highlight the known replicated associations and discuss outstanding challenges for the field. Issues relating to heterogeneity, power and technical variation significantly affect the results of mbGWAS. Hence, it is clear that a strategy of merely collecting larger and larger cohorts must be accompanied by further refinements in approach and analyses in order to yield more genetic insights into these interactions.

As such, the authors suggest some best practices and further directions for the field. These include increasing power through combining studies or traits analyzed and using the alternative phenotypes of microbial genetic variation (single-nucleotide polymorphisms or structural variation) to obtain robust new insights. Additional dimensions that relate to microbial function more directly, such as the level and composition of metabolites (actual microbial products), metatranscriptomics or metaproteomics, can be analyzed. Finally, extending analyses to non-bacterial species (viruses, fungi and protozoa) is likely to lead to further discoveries that will combine to give us a more complete picture of human host and microbiome interactions.

We are excited to see what the future brings for mbGWAS and are eager to see the full creativity and efforts of the human complex trait genetics community be deployed for the study of these complicated and fascinating microbial traits. ❐

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