Can the Human Microbiome be Targeted for Prevention/Therapy of Allergic Disease?

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Targeting the Human Microbiome for Allergies
Number Trends in Publications

‘Human Microbiome’
‘Cloak’ of Microbiota

Rethinking heritability of the microbiome

How should microbiome heritability be measured and interpreted?

By Edward J. van Opstal* and Seth R. Bordenstein†

For almost a century, heritability has been routinely used to predict genetic influences on phenotypes such as intelligence, obesity, 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/on the human body. This question has become increasingly interesting as research reveals that humans and their microbial communities interact in complex and often beneficial ways. 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.

Two main studies provide one method for quantifying heritability (2) of microbial taxa. In such analyses, heritability is measured by comparing variation in microbial taxa abundance that is attributable to human genetics. This approach simplifies microbial abundance 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 markers (2), or low overall gut microbiome heritability (3), respectively. But in 2016, the largest twin cohort to date examined members of the gut microbiome and found that the bacterial family Bacteroidaceae had the highest heritability (4<sup>≤</sup>3.06) and associate 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 it the only term to measure and denote microbiome heritability?

Under a heritability analysis with standard statistical approaches (such as the Additive Genetic, Common Environment, Unique Environment (AGE) model), the abundance of each human-associated microbe is presented as a continuously varying, quantitative trait that is affected by both genetics and the local environment. In other words, the host genotype 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 desirable 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 inter-specific (genotype-by-genotype) interactions that drive the assembly of the host and microbial consortia. It also necessitates the use of a measure—“community heritability” (5)—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 secondarily influence their own colonization of specific human genotypes. These features can compete for niche acquisition, mechanisms to evade the host immune system, and niche construction, among others. Thus, heritable taxa such as *Escherichia coli* may be “re-coded” by the human genome to perform beneficial functions in the microbial community, but they also may encode traits that enable them to disarm host defenses and colonize susceptible genotypes. For example, commensal bacteria may evade or evade human immune responses by modifying surface...
Human Genetic Inheritance

Microbial Inheritance

Environmental microbes
Family, etc...

Faith JJ et al PNAS 2014
Abundances of Phyla of Bacteria Genera
1st and 3rd Trimester of Pregnancy

Dramatic remodelling over the course of pregnancy

Koren O et al. Cell 2012
Most of the early colonizers are derived from the mother

Vertical mother-infant transmission was frequent for important intestinal microbes such as Bacteroides and Bifidobacterium
Meta-analyses of cohort and case-control studies find a positive association with:

- **type 1 diabetes** (based on 20 studies),
- **asthma** (23 studies),
- **obesity** (nine studies).

We did not find any meta-analyses that reported no association with these outcomes.
What are the consequences of the disappearing human microbiota?

Martin J. Blaser and Stanley Falkow

'heirloom' microbes

Nature Reviews Microbiology 2009
Peak:Trough ratio

New type of metagenomic analysis:
Provides an accurate quantitative estimate of the growth dynamics of the microbiota
**Growth dynamics vs Relative abundance**

**Tissue/organ “A”**

In a given tissue in an individual, an abundant microbial species may not necessarily be one with high metabolic activity (PTR value).

<table>
<thead>
<tr>
<th>BACTERIA</th>
<th>ABUNDANCE</th>
<th>GROWTH RATE (PTR VALUE)</th>
<th>METABOLIC ACTIVITY</th>
<th>DISEASE CORRELATION</th>
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<td>1.2</td>
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<tr>
<td>Species “2”</td>
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<td>2.0</td>
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Diet, Metabolites and ‘Western Lifestyle’ Inflammatory Diseases

Maintaining the Microbiome?

Thorburn A et al Immunity 2014
World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics

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Abstract

Background: Prevalence of allergic diseases in infants, whose parents and siblings do not have allergy, is approximately 10% and reaches 20–30% in those with an allergic first-degree relative. Intestinal microbiota may modulate immunologic and inflammatory systemic responses and, thus, influence development of sensitization and allergy/proposal.

Objectives: recommendations about the use of probiotics in the prevention of allergy.

Methods: We identified the most relevant clinical questions and performed a systematic review of randomized controlled trials of probiotics for the prevention of allergy. We followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to develop recommendations. We searched for and reviewed the evidence about health effects, patient values and preferences, and resource use (up to November 2014). We followed the GRADE evidence-to-decision framework to develop recommendations.

Results: Currently available evidence does not indicate that probiotic supplementation reduces the risk of developing allergy in children. However, considering all critical outcomes in this context, the WAO guideline panel determined that there is a likely net benefit from using probiotics resulting primarily from prevention of eczema. The WAO guideline panel suggests: a) using probiotics in pregnant women at high risk for having an allergic child; b) using probiotics in women who breastfeed infants at high risk of developing allergy; and c) using probiotics in infants at high risk of developing allergy. All recommendations are conditional and supported by very low quality evidence.

Conclusions: WAO recommendations about probiotic supplementation for prevention of allergy are intended to support parents, clinicians and other health care professionals in their decisions whether to use probiotics in pregnancy and during breastfeeding, and whether to give them to infants.

Keywords: Allergy, Prevention, Probiotics, Practice guidelines, GRADE

Probiotic supplementation **DOES NOT** reduce the risk of developing allergy in children

There is a likely net benefit from using probiotics resulting primarily from **prevention of eczema**

For at risk infants
a) in **pregnant women**;
b) in **women who breastfeed** infants

In **infants** at high risk of developing allergy.

All recommendations are **conditional** and supported by very **low quality evidence**.
Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis

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**Probiotic mixture**

**Single Probiotic**
ALLERGIES

- Genetics/Epigenetics
- Allergens
- Human microbiome
- Infection/Antimicrobials
- Pollution
- Lifestyle