



# “Nature versus Nurture” and the indigenous microbiome

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The human microbiome represents the total aggregate of microorganisms within the human body and is recognized as a significant player in human health and disease. The total number of bacteria in humans is nearly  $4 \times 10^{13}$ , and although recalculated appraisals of the ratio between human cells and microorganisms has now been reduced and approximates 1:1, the vast quantity of bacteria has an enormous impact in host physiology (1). Healthy development and disease states are closely entwined with the microbiome and examples include obesity, cancer, and also include conditions outside the gastrointestinal tract, such as neurologic and psychiatric illness (2-6). Therefore, understanding the influences on the microbiome is critical to appreciating possible preventative and therapeutic measures for disease.

There is a large body of evidence implicating a role for the environment in shaping the microbiome which can have long-lasting consequences. At birth, the mode of delivery (Cesarean section versus vaginal delivery) is one of the earliest environmental factors in determining the gastrointestinal microbiome (7). Oral antibiotic regimens radically alter the gastrointestinal microbiome, in some cases causing overgrowth of bacteria that can be harmful, as in *Clostridium difficile* in pseudomembranous colitis (8,9). Likewise, an individual's diet has a huge impact in modifying the microbiome (10).

The article by Bonder et al., describes how differences in host genetics are associated with the differences in the residential microbiota (11). Using three Danish cohort studies and metagenomic shotgun sequencing, the group analyzed the fecal microbiome in 1,514 human subjects after receiving a matched blood sample that was genotyped. Enrolled subjects were examined for single

nucleotide polymorphisms (SNP) that had a minor allele frequency  $>0.05$  and this was compared with their respective fecal microbial taxonomies. Fifty-eight SNPs at 9 loci were associated with specific microbial taxa. Of note, the authors showed a significant association with the *Blautia* genus and the *Methanobacteriaceae* family, which has been implicated in inflammatory bowel disease, obesity and dyslipidemias (12). Other genetic associations that were discovered included the species *Dialister invisus*, which has a role in gut inflammation, and *Sutterellaceae* abundance (13). Furthermore, they showed that there were specific loci that were associated with certain microbial metabolic pathways, specifically in the degradation of plant sterols and bile acid metabolism. These functional units are believed to have roles in obesity, type 2 diabetes and the metabolic syndrome. Interestingly, the genetic variants that were associated with these metabolic pathways were not the same variants involved in microbiota taxonomic differences, suggesting that different host loci influence taxonomic differences and functional pathways largely independently. Focused analyses examining specific genes involved in immunity found associations with IBD-associated bacteria, notably *Proteobacteria* and *Coprococcus comes*. Similar approaches to metabolic loci also demonstrated associations, including *Lactococcus* and an SNP involved in fat distribution.

One of the most interesting aspects of the study was associations between different microbiota with specific loci of C type lectin receptors. C type lectin receptors, along with other receptors have a critical role in immunity and inflammation. Specific polymorphisms in *CLEC7A* gene have been associated with more severe inflammatory disease

in ulcerative colitis (14).

Evidently, the microbiota is both influenced by host genetics and environmental exposures. This study highlights how SNP correlates with differences in the GI microbiome as determined from fecal samples. Whilst the subjects' diet was recorded in the study, exactly how this was controlled for is not clear and whether microbiota differences could have manifest through dissimilar dietary intakes is a possibility. This is also true with other environmental influences on the microbiome, which may not have been controlled for, such as smoking and exercise (15,16).

Certainly, the issue of host genetics on the microbiota is complex and large-scale studies are required to overcome the small effect sizes that individual SNP may have on the microbiota. Extension of this work into examining the microbiota of the skin, vagina, oral and nasal cavities would be worthwhile to further document the role of host genetics in the microbiota at these sites. With more investigation of host genetics and their interaction with the microbiome, we will be able to better understand complex diseases and provide therapeutic options against harmful dysbiosis.

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