How human genes affect the microbiome

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Our genes determine to some extent which bacteria live in our intestines. Studies on human twins and experimental work with animals have both confirmed that our microbiome is partly hereditary. But so far, there was only limited information about the host genes that affect the microbiome. Now a new study, led by the University Medical Center Groningen/University of Groningen Department of Genetics has associated genetic loci and specific genes in human DNA to bacterial species and their metabolic signatures. The results have been published in the journal *Nature Genetics* on October 3rd.

An international team of geneticists used three large Dutch cohort studies to identify genes affecting the microbiome. First, an association study was performed in the University Medical Center Groningen's Lifelines-DEEP cohort, on 984 participants. Stool samples from this cohort were analyzed by metagenomic sequencing, which was used both to identify micro-organisms and to help determine their functions. These data were then correlated to genetic, phenotype and dietary information from all the participants. Next, the results were replicated in two smaller Dutch cohorts: the Radboud University Medical Center's 500FG study cohort (425 participants) and the Maastricht University Medical Center's MIBS cohort (105 participants).

'To our knowledge this is the largest metagenome dataset to date', says first author Marc Jan Bonder. 'And the use of metagenomic sequencing to get information about both the abundances of the micro-organisms and their functions makes this study unique. We were able, in this large population of volunteers, to link microbial variation to genetic variation.'

Milk intake

One particularly interesting finding was the association between genetic variants that determine the presence of lactase in adults and the presence of Bifidobacterium in the gut. Lactase deficiency causes lactose intolerance. 'Surprisingly enough, we found no difference in overall milk intake by individuals with or without the hypolactasia predisposing genotype', says principal investigator Dr. Alexandra Zhernakova. But, for individuals without the functional lactase gene, the numbers of Bifidobacterium increased with a higher consumption of dairy products.

A possible explanation for these results is that Bifidobacterium, which can break down lactose, rescues lactase-deficient individuals from lactose intolerance. 'As the bacterium is ingested through milk, it appears that these individuals can actually continue drinking milk if it causes no complaints', says Zhernakova.

Immune system

Another association was found with variants of the C-type lectin genes. These genes code for receptors that recognize different species of bacteria and fungi, and they guide the cytokine response to these micro-organisms. Zhernakova: 'These receptors are part of the innate immune system. Several other innate immunity genes also showed association with certain taxonomies and bacterial pathways, although these associations were weaker. This means the C-type lectin receptors could be an interesting target for treatments aimed at modifying the microbiome'.

The scientists also looked for association with specific genes from the HLA system, which is part of the body's adaptive immune system that is developed through encounters with micro-organisms. 'Surprisingly, gene variants from the HLA system showed very little correlation with the microbiome', says Zhernakova.

Diseases

This study provides a first glimpse into how our genes affect the microbiome. Such correlations are of interest for many multifactorial diseases that are affected by genes, the microbiome, and environmental factors like diet. Bonder: 'This type of research will also help us to provide personalized health advice, for example, what we can now tell individuals with lactase deficiency.'

More information: The effect of host genetics on the gut microbiome, nature.com/articles/doi:10.1038/ng.3663

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