The Gene–Microbe Link

Evidence that genes shape the microbiome may point to new treatments for common diseases *By Ruth E. Ley*

The ecology of the gut microbiome may trigger or contribute to a variety of diseases, including autoimmune disorders and obesity, research suggests. Factors such as early environment, diet and antibiotic exposure have a lot to do with why people differ from one another in the composition of their microbiomes. But specific gene variants are also linked to greater risks of developing many of these diseases. Do your genes act on your microbiome, which in turn promotes disease?

One way researchers have addressed this question is to pick specific genes that are good candidates—for instance, those with a strong link to a disease that also has a microbiome link—and examine whether people who carry mutations that are known to increase the risk of a certain disease also have microbiomes that differ from those who do not have the mutations. A team led by Dan Frank at the University of Colorado Denver took this approach and revealed that specific variants of the *NOD2* gene that confer a high risk of developing inflammatory bowel disease to their carriers are also associated with an altered intestinal microbiome.

A powerful and broader way to look for an effect of human genetic variation on the microbiome is to compare twins. Identical twins share nearly 100 percent of their genes; fraternal twins, 50 percent. Co-twins are raised together, so the environmental effects on their microbiomes should be about the same. If the microbiomes of the identical twins are more alike within a twinship than those of the fraternal twins, we can conclude that genes have played a role. If variation within twinships of each kind is about the same, we can say a shared genome has had no additional effect.

A powerful way to look for an effect of human genetic variation on the microbiome is to compare twins.

Early twins studies were based on fewer than 50 twin pairs and could not detect any greater similarities in the microbiomes of identical twins compared with those of fraternal twins. But recent work my laboratory at Cornell University conducted with researchers at King's College London compared nearly 500 twin pairs, a sample size sufficient to show a marked genetic effect on the relative abundance of a specific set of gut microbes. Furthermore, so-called heritable microbes—the bacteria most influenced by host genetics—were more abundant in lean twins than obese ones.

Experiments in germ-free mice showed that one gut bacterium in particular, *Christensenella minuta,* can influence the phenotype—the composite of observable characteristics or traits—of the host. Germ-free mice live in sterile bubbles—and they are very skinny. When they are given a microbiome in the form of a fecal transplant from a human donor, however, they plump up within a day or two because the bacteria help them digest their food and develop a proper metabolism. We found that if *C. minuta* was added to the feces of an obese human donor, the recipient mice were thinner than when *C. minuta* was not added. Results showing *C. minuta* has an effect of controlling fat gain in the mouse match data that reveal lean people have a greater abundance of *C. minuta* in their gut than obese people.

This is evidence that a person's genes can influence the gut microbiome's composition and in turn can shape the individual's phenotype. Further work will show what specific genes are involved as well as how the microbiome may be reshaped to reduce risk of developing chronic inflammatory diseases within the context of a person's genotype, suggesting potential new approaches to treating obesity-related diseases.

Ruth E. Ley *is an associate professor of molecular biology and genetics at Cornell University.*

ILLUSTRATION BY GLUEKIT