In a first, scientists map the genetic diversity of microbes residing in the human gut and mouth

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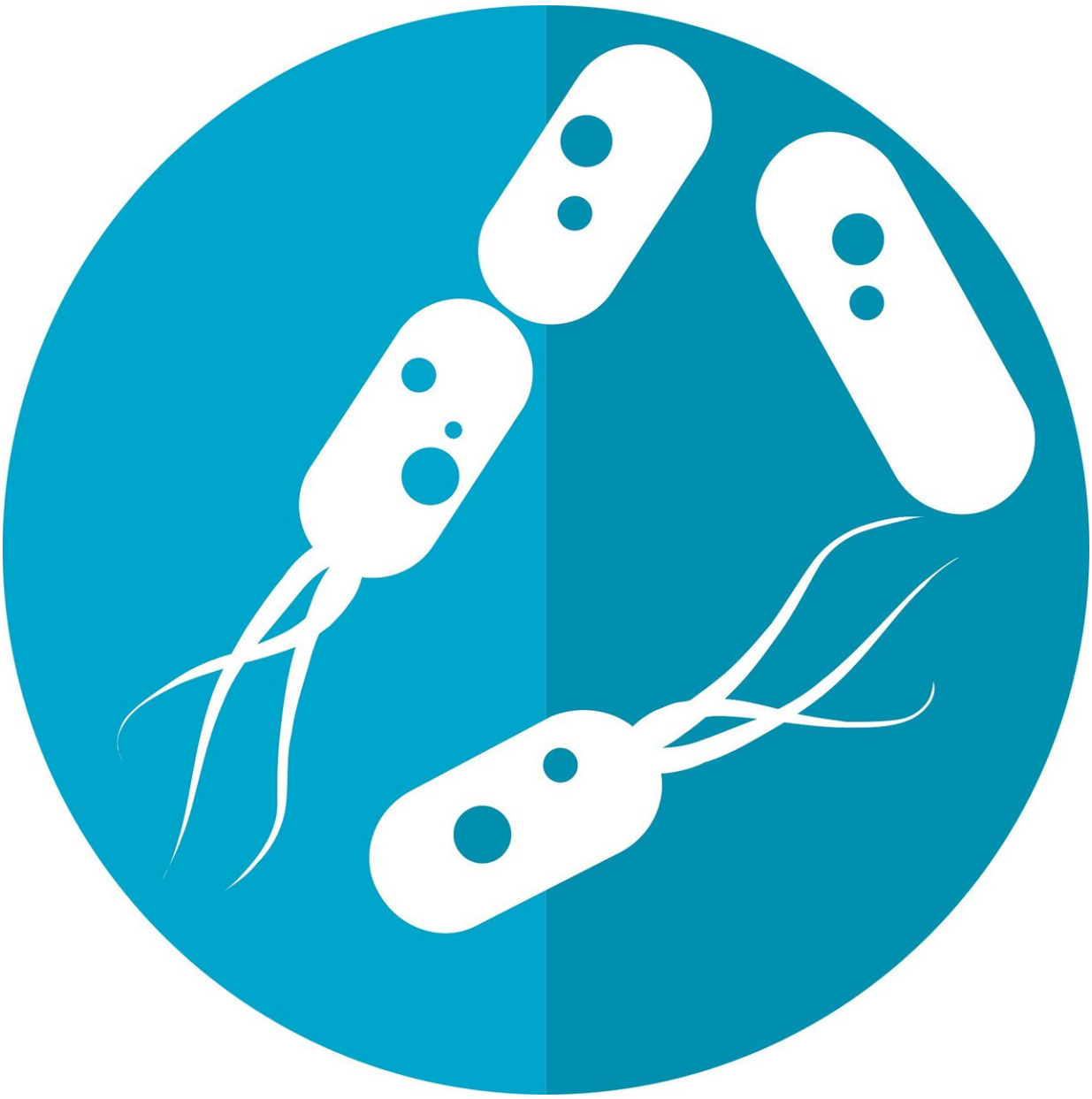

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How many stars are there in the observable universe? It was once deemed an impossible question, but astronomers have gleaned an answer—about one billion trillion of them.

Now, scientists at Harvard Medical School and Joslin Diabetes Center have embarked on what could be a similarly daunting quest: How many genes are there in the human microbiome?

In a study published Aug. 14 in the journal *Cell Host & Microbe*, a team of microbiologists and bioinformaticians offer a first glimpse of the array of genes that make up the bacterial universe residing in each of us.

The findings thus far: There may be more genes in the collective human microbiome than stars in the observable universe, and at least half of these genes appear to be unique to each individual—a diversity far exceeding the researchers' expectations.

The research is believed to be the largest analysis of its kind to date and the first one to include DNA samples from bacteria that reside both in the mouth and the gut. Past studies have focused on one or the other.

Even so, the work marks only the beginning of efforts to analyze the entire genome of the human microbiome.

"Ours is a gateway study, the first step on a what will likely be a long journey toward understanding how differences in gene content drive microbial behavior and modify disease risk," said study first author

Braden Tierney, a graduate student at Harvard Medical School.

Microbial fingerprinting for more precise therapies

Scientists estimate that the human microbiome—the collective body of microbes that populate our guts, mouths, skin and other parts of the body—contains trillions of bacteria, most of them harmless, many beneficial and some disease causing. Mounting evidence has revealed the role of these microbes as powerful modulators of disease and health. Changes in both bacterial count and bacterial content have been linked to development of conditions ranging from garden variety dental caries and gut infections to more serious ones, including chronic inflammatory bowel disease, diabetes and multiple sclerosis.

Most research to date has focused on mapping the types of bacteria that inhabit our bodies in an effort to determine whether and how the presence of a given bacterial species might affect disease risk. By contrast, the new research delves far deeper, looking at the genes that make up the various microbial species and strains.

Studying bacterial species alone is bound to provide only partial clues into these microorganisms' role in disease and health, the researchers say. Given that genetic content varies greatly between the same microbes, understanding how and whether individual microbial genes affect disease risk is just as important.

"Just like no two siblings are genetically identical, no two bacterial strains are genetically identical, either," said study co-senior author Chirag Patel, assistant professor of biomedical informatics at Harvard Medical School's Blavatnik Institute. "Two members of the same bacterial strain could have markedly different genetic makeup, so information about bacterial species alone could mask critical differences that arise from genetic variation."

Cataloguing the array of microbial genes could inform the design of precision-targeted treatments, said study senior co-author Alex Kostic, assistant professor of microbiology at Harvard Medical School and an investigator at the Joslin Diabetes Center.

"Such narrowly targeted therapies would be based on the unique microbial genetic make-up of a person rather than on bacterial type alone," Kostic said.

Additionally, profiling the unique genes that make up a person's microbiome could act as a form of microbial fingerprinting that provides valuable clues about past exposures to different pathogens or environmental influences, as well as disease predispositions, Kostic added.

A microbe's evolutionary organ

In the study, the researchers set out to estimate the size of the universe of microbial genes in the human body, gathering all publicly available DNA sequencing data on human oral and gut microbiomes. In total, they analyzed the DNA of some 3,500 human microbiome samples, of which more than 1,400 were obtained from people's mouths and 2,100 from people's guts.

There were nearly 46 million bacterial genes in the 3,500 samples—about 24 million in the oral microbiome and 22 million in the gut microbiome, the researchers found.

More than half of all the bacterial genes (23 million) occurred only once, rendering them unique to the individual. The researchers termed these unique genes "singletons." Of the 23 million singletons, 11.8 million came from oral samples and 12.6 million came from intestinal samples.

Compounding the intrigue, these singleton genes also appeared to behave differently from other genes, the researchers observed: they performed different functions.

Commonly shared genes, the analysis showed, appeared to be involved in more or less basic functions critical to a microbe's day-to-day survival, such the consumption and breakdown of enzymes, energy conversion and metabolism. Unique genes, by contrast, tended to carry out more specialized functions, such as gaining resistance against antibiotics and other pressures and helping to build a microbe's protective cell wall, which shields it from external assaults.

This finding, the team said, suggests that singleton genes are key parts of a microbe's evolutionary survival kit.

"Some of these unique genes appear to be important in solving evolutionary challenges," Tierney said. "If a microbe needs to become resistant to an antibiotic because of exposure to drugs or suddenly faces a new selective pressure, the singleton genes may be the wellspring of genetic diversity the microbe can pull from to adapt."

But what fuels such gene diversity?

The answer to this question remains the subject of further research, the investigators said, but they believe there are at least two important drivers of genetic variation.

One is the microbes' love of freely swapping DNA material with their neighbors—a phenomenon known as horizontal gene transfer. To test this hypothesis, the researchers performed a special type of analysis that detects the shared molecular content between two organisms. To their surprise, they found little evidence that horizontal gene transfer was a main source of genetic uniqueness. Indeed, less than 1 percent of unique

genes detected in oral samples and just under 2 percent of those found in the gut appeared to have arisen through this neighborly gene exchange.

Therefore, the researchers hypothesize, another, more powerful, driver of genetic diversity could be bacteria's ability to evolve their DNA rapidly in response to changes in the host environment. The current study was not designed to detect the precise environmental changes that drive this variation, but examples of such changes may include what type of food a person consumes, what medication they use, the lifestyle choices they make, what environmental exposures they encounter and any physiologic changes in the host, including upregulation and downregulation in various host genes or whether a person develops a disease.

So how many genes in the collective human microbiome?

By one calculation, that number could be around 232 million, the study estimated. Another estimate, however, yielded a number comparable to the number of atoms in the universe.

Indeed, the true number may be unknowable, Patel said.

"Whatever it may be, we hope that our catalog, along with a searchable web application, will have many practical uses and seed many directions of research in the field of host-microbe relationships."

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