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Bacteria may have endless diversity

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Individual strains of the bacterium *Streptococcus agalactiae* show so much diversity that sequencing even hundreds of genomes may not reveal all the genes present in the species, according to a study published in last week's early online edition of the *Proceedings of the National Academy of Sciences (PNAS)*. This variation likely arises because bacteria easily take up DNA from their environment, through horizontal gene transfer and bacteriophage infection, according to the study's authors. The new report also suggests that current methods of characterizing bacterial strains may not capture their genetic relationships.

"It is potentially a landmark paper regarding pathogen evolution," said Fiona Brinkman of Simon Fraser University in Burnaby, British Columbia, who was not involved in the study. One of the study's biggest implications is that there seems to be a surprisingly vast "pool of genes out there in the environment for bacteria to draw upon," Brinkman said.

Most genome projects have only sequenced one or two genomes from any species, said the study's first author Hervé Tettelin of the Institute for Genomic Research in Rockville, Md., which makes it difficult to determine how much diversity exists between individuals. As part of this study, Tettelin and his colleagues sequenced six strains of S. agalactiae—also known as group B *Streptococcus*, or GBS—and compared these sequences with each other and with two strains whose genomes had been sequenced previously. These eight genomes covered all five of the major disease-causing serotypes in the United States and Europe, Tettelin said.

The researchers found that each of the eight strains contained unique genes. About 80% of the GBS genome was conserved in all eight strains, while the other 20% was either partially shared or specific to only one strain.

Tettelin and his co-workers then calculated how many new genes appeared with each additional strain sequenced. Considering all possible permutations, they found that a second GBS genome adds, on average, 161 genes not present in the first strain, whereas the fifth genome adds only 54 novel genes. Extrapolating these data revealed a decaying exponential curve that bottoms out at 33 new genes per genome sequenced. "Because it plateaus at that value, we can't predict how many genomes we'd have to sequence to have found all the genes that contribute to that GBS species," Tettelin said. "I doubt it's infinite, but it could be very large."

"I'm not convinced you can extrapolate from eight to infinity," said Frederick Blattner of the University of Wisconsin-Madison, who was not involved in the research, adding that it is believable that an extremely large number of GBS genomes would be needed to encompass all available genes. Previous work in *Escherichia coli* has also shown immense diversity between strains, Blattner said, likely arising from lateral gene exchange.

Genetic heterogeneity in GBS strains also probably comes from horizontally transferred DNA, Tettelin said. Many of the strain-specific genes showed atypical nucleotide composition, which hints that these regions originated in species with different nucleotide content, Tettelin said. They also found that 10% of all strain-specific genes in GBS are associated with bacteriophages.

"It seems very likely that most of this diversity that they're seeing in the genome sequences came by horizontal gene transfer," said Daniel Zeigler, director of the Bacillus Genetic Stock Center at Ohio State University.

Researchers tend to think of bacteria "as just existing in splendid isolation out there in the environment," Zeigler told *The Scientist*, but "the way we need to think about them is in a very dynamic environment, where there's genetic information constantly being exchanged."

The authors also examined genome sequences of five strains of *Streptococcus pyogenes* (group A *Streptococcus*) and found that each additional genome adds new genes. When they performed the same test with eight strains of *Bacillus anthracis*, however, they found that just four genomes captured all the genes found in any strain.

This may be because humans have purposefully selected the most virulent *B. anthracis*, Tettelin said, so all of this species "could be a very small clone of the whole diversity of the *Bacillus cereus* group" from which *B. anthracis* derives, Tettelin told *The Scientist*. Another possibility, though, is that "this bug is just not that good at acquiring anything from the outside." Higher organisms probably do not have this much genomic diversity, either, because they do not exchange as much DNA horizontally with other species, said Zeigler.

Tettelin and his colleagues also showed that GBS serotypes, a common method of characterizing bacterial strains, do not correlate with genetic relationships determined by genome sequencing. This finding is not surprising, Blattner said, because "the serotype is just one antigenic determinant." It does suggest that methods of typing bacteria may have to change, according to Brinkman. With current typing methods, she said, "we're really not truly seeing the kind of bacterial diversity that exists out there."

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