# Distinguishing deadly Staph bacteria from harmless strains

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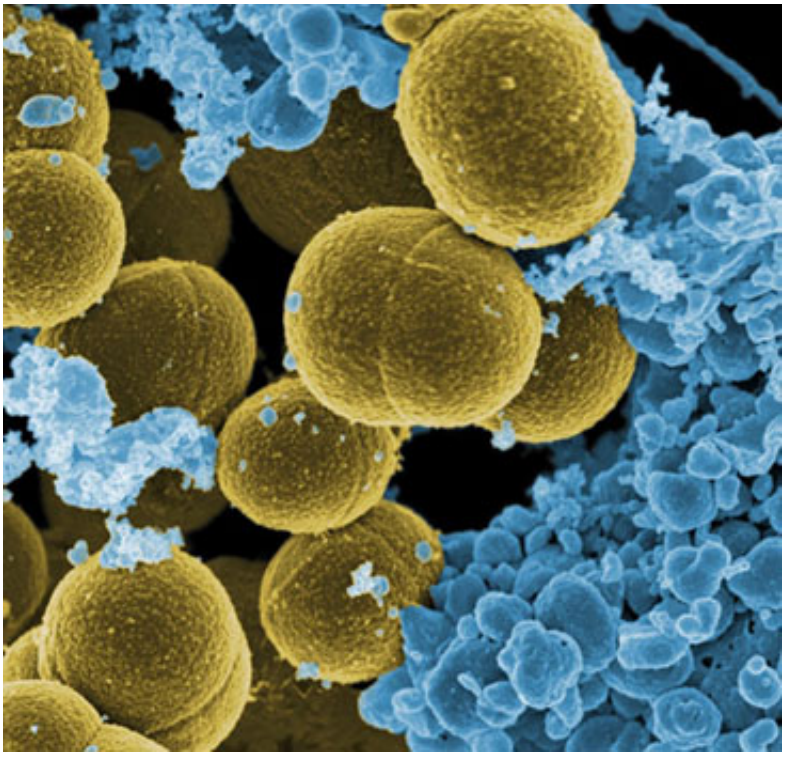

The *Staphylococcus aureus* pan-genome -- a survey of 64 strains -- is made up of a "core" genome and a "dispensable" genome. Credit: NIAID

*Staphylococcus aureus* bacteria are the leading cause of skin, soft tissue and several other types of infections. Staph is also a global public threat due to the rapid rise of antibiotic-resistant strains, including methicillin-resistant *Staphylococcus aureus* or MRSA. Yet Staph also commonly colonize our nasal passages and other body sites without harm. To better

understand these bacteria and develop more effective treatments, University of California San Diego researchers examined not just a single representative Staph genome, but the "pan-genome"—the genomes of 64 different strains that differ in where they live, the types of hosts they infect and their antibiotic resistance profiles.

This effort, published June 6 by the *Proceedings of the National Academy of Sciences*, places all Staph genes into one of two categories: the core genome or the dispensable genome.

The study resulted from a collaboration between Bernhard Palsson, PhD, Distinguished Professor of Bioengineering and Pediatrics, and Victor Nizet, MD, professor of pediatrics and pharmacy. Experiments were mostly performed by Jonathan Monk, then a graduate student in Palsson's lab.

"The most exciting thing about this study is the computational ability to analyze so many strains simultaneously—an unlimited number, really—to better understand the interrelationships between fundamental metabolism of the organisms and its virulence, or ability to cause human disease," said Nizet, a pediatrician and infectious disease researcher.

Palsson is a pioneer in systems biology, a scientific field that combines experimental and computational methods to capture a multi-layered view of complex living systems and how they work. In this study, Monk and Palsson used genome-scale models—computer simulations—of Staph metabolism to systematically analyze the ability of 64 Staph strains to thrive in more than 300 different environments.

On average, a single Staph genome encodes 2,800 genes. But here the researchers found a total of 7,457 genes across 64 strains of the bacterium—the Staph pan-genome. Nineteen percent of the pan-genome (1,441 genes) made up what the team calls the "core genome," referring

to the genes essential for life and encoded by all strains. In contrast, the vast majority of the Staph pan-genome was dispensable, and more variable across strains—39 percent (2,871 genes) were deemed "accessory," meaning they were present in some but not all strains, and the remaining 42 percent (2,871 genes) "unique," meaning they were found in only one strain.

Dispensable genes give the strains that possess them advantages under particular environmental conditions, such as adaption to distinct living spaces, the ability to colonize new human or animal hosts and antibiotic resistance.

"Knowledge from a single strain is never sufficient to represent an entire species," Palsson said. "Now, the Staph pan-genome could help us be smarter about our analyses of bacterial virulence and how bacteria respond to or resist antibiotics."

"This study provides an essential roadmap—one that describes what it means to be *Staphylococcus aureus* ," Nizet said. "We can now use this information to test any number of hypotheses. For example, we might identify a system that's essential for the bacterium's life and now we can take that information back to the lab, study those genes and the proteins they encode in depth, and screen for new therapeutics that specifically target that pathway."

Palsson and Nizet recently received a five-year, $9.5-million award from the National Institute of Allergy and Infectious Diseases at the National Institutes of Health to establish an interdisciplinary center to define the systems biology of antibiotic resistance.

**More information:** Comparative genome-scale modelling of Staphylococcus aureus strains identifies strain-specific metabolic capabilities linked to pathogenicity, *PNAS*,

www.pnas.org/cgi/doi/10.1073/pnas.1523199113