Using SNPs to decode anthrax

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Bacillus anthracis, commonly referred to as anthrax, has been a tough microbe to crack genetically because its strains exhibit minimal variation worldwide. But a new bacterial typing system developed by researchers at the Northern Arizona University (NAU), the Translational Genomics Research Institute (TGen) and The Institute for Genomic Research (TIGR) has enabled them to detect minute variations among several anthrax isolates and holds potential for similar discoveries in other pathogens.

Evolutionary history

Anthrax does not appear to accumulate mutations at a high rate and most of the mutations that that occur are stable. As a result, genetic fingerprinting has failed to fully identify the group's phylogenic diversity [1]. 'Most strains differ by between 400 and not even 100 nucleotides out of 5 million,' says Jacques Ravel, an Assistant Investigator in Microbial Genomics at TIGR (http://www.tigr.org). 'You just can't access this diversity using [conventional] typing systems.'

Paul Keim, Cowden Endowed Chair in Microbiology at NAU (http://www.nau.edu) and Director of the Pathogen Genomics Division at TGen (http://www.tgen.org), recently led the development of a novel identification approach that was able to define the evolution of anthrax with remarkable accuracy [2]. 'We went through and picked out very different strains of *Bacillus anthracis* to sequence their whole genome,' he explains. SNPs, the single nucleotide polymorphisms or differences among strains, were identified and characterized.

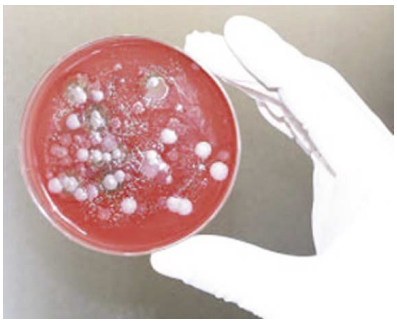
It turns out that anthrax has three major phylogenic lineages: the A branch is the most successful and accounts for 85% of all cases worldwide; the B1 and B2 branches account for ~15% of the total; and the C branch, which has evolved very slowly, is rare [2].

New detection model

The researchers mapped 990 of about 3,500 SNPs that were identified from five anthrax strain sequences [2]. By 'canonizing' redundant SNPs, essentially choosing one SNP to represent those that provide the same diagnostic information, the significant differences were summarized in 24 SNPs, says Keim. His laboratory has since used this information to develop diagnostic assays that can differentiate between two strains of anthrax at the single nucleotide level. 'The SNPs that we used to determine the evolution of anthrax fit right into a diagnostic strategy,' Keim says.

This has obvious implications for forensics, says Philip Hanna, Assistant Professor of Microbiology and Immunology at the University of Michigan Medical School (http://www.med.umich.edu/medschool/). 'They can use these SNPs to track strains and pinpoint them to other strains throughout the world.' Those involved in anthrax decontamination efforts also will be able 'to detect what strain it is very quickly,' says Ravel.

Further studies underway with plague suggest the same approach will work with it and other pathogens that pose bioterrorism or public health risks. 'You're developing tools for the forensics toolkit that could play an important role in [determining] how cholera travels around the world,' suggests Jennie Hunter-Cevera, President of the University of Maryland Biotechnology Institute (http://www.umbi.umd.edu/). Ultimately, this could lead those working in clinical microbiology and infectious diseases to develop 'prophylactic approaches, new class of antibiotics and perhaps even better vaccines', she adds.



Bacillis anthracis visible as white colonies on a petri dish with other bacteria. Image courtesy of P. Keim of the Northern Arizona University and the Translational Genomics Research Institute (http://www.tgen.org).

Drug discovery

These findings are good news for those working to develop an anthrax vaccine. 'It shows quite strongly that one strain may not be worse than another in causing disease,' says Hanna. 'They look very similar and the differences are mainly at the point of these SNPs that don't really change the way the bug interacts with its environment, its metabolism or its pathogenesis.'

References

1 Keim, P. *et al.* (2000) Multiple-locus variable-number tandem repeat analysis reveals genetic relationships within *Bacillus anthracis*. *J. Bacteriol.* 182, 2928–2936

2 Pearson, T. *et al.* (2004) Phylogenetic discovery bias in *Bacillus anthracis* using single nucleotide polymorphisms from whole genome sequencing. *Proc. Nat. Acad. Sci. U. S. A.* DOI: 10.1073/pnas.0403844101 (Epub ahead of print; http://www.pnas.org)

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