

BACTERIAL EVOLUTION

Parallel lives

The increased availability of high-throughput whole-genome sequencing has facilitated analysis of the transmission and evolution of bacterial pathogens during disease outbreaks. To date, however, it has been difficult to separate adaptive mutations, which confer a benefit, from neutral mutations, which have no impact on fitness. A new study published in *Nature Genetics* now reveals the parallel adaptive evolution of a bacterial pathogen during infection of humans and identifies new candidate pathogenicity genes.

Lieberman *et al.* undertook a retrospective analysis of a *Burkholderia dolosa* outbreak that occurred over a 16-year period in patients with cystic fibrosis. The genomes of 112 isolates from 14 patients were sequenced. Analysis revealed that SNPs accumulated at a consistent rate of about two per year over the course

of the outbreak. To investigate how the pathogen changed over this time, the authors first looked for SNPs in genes known to be associated with specific pathogenic phenotypes, namely antibiotic resistance and the presence of the O antigen (one of the components of lipopolysaccharide). Nonsynonymous mutations were detected in a homologue of the gene encoding DNA gyrase subunit A (*gyrA*), which confers resistance to ciprofloxacin, and in a glycosyltransferase gene involved in the production of O antigen repeats; these SNPs had arisen independently in several individuals, indicating strong positive selection.

The authors then used a systematic genome-wide approach to identify all of the *B. dolosa* genes that were under positive selection during infection. Calculating the number of independent mutational events in the genome showed that the distribution of SNPs was nonrandom, with 17 genes acquiring at least three nonsynonymous mutations in multiple individuals, including the two genes already analysed. All 17 genes were conserved across all

Burkholderia species examined. Of the 17 loci, 11 encoded proteins with strong connections to pathogenicity, including proteins involved in antibiotic resistance and membrane composition. The remaining six genes had not previously been associated with pathogenicity and comprised three genes encoding proteins involved in oxygen-dependent gene regulation and three genes encoding proteins of unknown function.

This study has identified the key pathways involved in the pathogenesis of this rare bacterial pathogen and so could have therapeutic implications. More importantly, perhaps, it represents another step towards a complete understanding of the adaptive changes that occur in clinically important bacterial pathogens when inside the human host.

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ORIGINAL RESEARCH PAPER Lieberman, T. D. *et al.* Parallel bacterial evolution within multiple patients identifies candidate pathogenicity genes. *Nature Genet.* **43**, 1275–1280 (2011)