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The Origin of a Killer Revealed by Bronze Age *Yersinia* Genomes

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Bubonic plaque is caused by *Yersinia pestis*, a deadly pathogen that left deep scars in human history. Rasmussen et al. (2015) have now retrieved *Y. pestis* genomes from 2,800- to 5,000-year-old human teeth, shedding new light on origins of the strain that brought Black Death to Europe 670 years ago.

Human history is marked with epidemics caused by bacteria. No encounter with bacteria left deeper scars in human memory than the bubonic plague (German: *die Pest*) that ravaged Europe during the years 1347–1351. Caused by strains of *Yersinia pestis* that were spread by fleas on rats, the first symptoms of plague were sneezing, followed by heavily swollen lymph nodes, fever, vomiting, and almost certain death, all within the course of about a week. The first symptom left a permanent mark in European language—a human sneeze still often prompts a well-meant "God bless you!" or "*Gesundheit*!" (German: health!)—while the swollen lymph nodes (buboes, from Latin *bubo*: groin) gave the plague its name. Today, plague can be treated with antibiotics. But the trauma of the plague sits deep, and humans still strive to better understand what, exactly, happened to us when Black Death descended upon Europe and why the encounters with *Y. pestis* were so devastating.

Important new chapters in the history of plague are published in the latest issue of *Cell*, where Rasmussen and colleagues (Rasmussen et al., 2015) report genome sequences of *Y. pestis* strains obtained from 2,800- to 5,000-year-old human remains from archaeological site across Europe and Asia. Their findings suggest that the virulent, flea-borne *Y. pestis* strain that caused the historic bubonic plague pandemics evolved from a less pathogenic *Y. pestis* lineage that was infecting human populations long before recorded evidence of plague outbreaks. The new metagenomic data stems from human teeth obtained from well-preserved human remains at a number of accurately dated archaeological sites. The new study constrains the timeline on the origin of traits that turned *Y. pestis* into a killer.

The practice of studying past epidemics with ancient DNA started in 1998 with a paper from Didier Raoult's laboratory in Marseille (Drancourt et al., 1998), a paper that itself has a small history (Raoult, 2016). The Raoult lab, long a leading address in the field of medical microbiology, was going about the business of investigating human pathogens when Olivier Dutour, an anthropologist who had been excavating a mass burial site from the plague of Marseille from the year 1720, popped up in the department with a box of bones from the excavation site—a possible source of ancient plague DNA. Interesting. At the same time, a young dentistry student from the medical faculty, Gérard Abhoudharam, turned up looking for a project that one could handle in a modest time frame. Raoult reasoned that teeth, which harbor a small but heavily vascularized organ called the pulp, might have contained enough blood at the time of death to have preserved remains of the systemic *Yersinia* infection that brought the plague victims to their grave. They were able to amplify some *Yersinia*-specific sequences from that ancient pulp DNA, and that was the beginning of ancient bacterial pathogen studies, or palaeomicrobiology.

As is typical for the field of ancient DNA studies, the report of Drancourt et al. (1998) was followed by much controversy (Raoult, 2016), and some investigators were unable to recover *Yersinia* sequences from similar teeth. Rasmussen et al.'s new report resolves that old controversy for good. They generated tooth metagenomic data from the remains of 101 individuals and found that only seven harbored *Yersinia* genomes. Those genomes are furthermore different, and they also recovered an eighth genome that is related to *Yersinia* but does not represent an ancestor of the pathogen. That not only rules out the possibility that some systemic contamination underpinned their result, but it also reveals that, when it comes to recovering DNA from ancient plague victims, not all teeth are equal. Rasmussen et al. took particular care to show that their sequences represent true ancient *Yersinia* strains, including a comparison of the decay rate in the *Yersinia* DNA to that in human DNA stemming from the same sources.

The perhaps most convincing evidence for the veracity of the data, and at the same time, the richest source of insights into plague evolution, are the lack of specific mutations and plasmids that make *Yersinia pestis* flea-borne, rodent-transmitted, and fatal to humans. The Bronze age samples lacked the gene for *Yersinia* murine toxin, *ymt*, which resides on the pMT1 plasmid and allows the bacterium to live in insect guts. The *ymt* gene is important, as it allows *Yersinia* to spread using arthropods as vectors. Three ancient samples lacked the pMT1 plasmid altogether (Rasmussen et al., 2015), and the *ymt* gene is missing in *Yersinia* samples older than 3,700 years, but is present in 98% of strains that are younger than 3,000 years. This suggests a relatively recent and very rapid spread of the *ymt* gene. And for any skeptics who might doubt the importance of lateral gene transfer in evolution, the *ymt* gene is flanked by transposons, both in the first copy of the *Y. pestis* plasmid sequenced (Lindler et al., 1998) and in the ancient samples (Rasmussen et al., 2015). In addition, the ancient strains lack important loss-of-function mutations

(Rasmussen et al., 2015) recently shown to be essential for transmission by fleas (Sun et al., 2014), indicating that the Bronze Age *Y. pestis* strains were not flea transmitted.

How pathogenic were these ancient *Y. pestis* strains? The most ancient ones lack the isoleucine to threonine mutation at position 259 in the Pla protein, a mutation that has been shown to be essential for developing bubonic, but not pneumonic, plague (Zimbler et al., 2015). The new genomes—if we can call Bronze Age genomes "new"—report important insights into virtually all of the genes currently known to be involved in *Y. pestis* pathogenicity (Rasmussen et al., 2015). This provides a uniquely documented historical record of events in *Yersinia* genome evolution, allowing us to date the appearance of functionally relevant mutations. The well-dated nature of the remains that harbor these *Yersinia* strains furthermore puts very robust constraints on the timeline of *Yersinia* evolution, which has been an issue of considerable interest lately (Wagner et al., 2014).

There is a rich history of recurrent plaque epidemics during recorded human history going back to Roman times (Drancourt and Raoult 2002). The new findings indicate that humans have been exposed to *Y. pestis* for much longer than any previous historical record suggested. Indeed, prior work had not provided direct molecular evidence for *Y. pestis* biology from material older than 1,500 years (Bos et al., 2011; Wagner et al., 2014). The new findings are thus an important milestone that pushes the record of plague evolution back by thousands of years, filling in gaps in our understanding of what happened during one of humankind's most traumatic encounters with microbial growth.

It wasn't long ago that movies brought the horrific image of genetically resurrected, meat-eating dinosaurs into our lives. With these new 5,000-year-old bacterial genome sequences, and the capabilities imparted by modern genome synthesis, we are closer than ever before to being able to bring the genomes of the dead back to life. Our past is catching up with us quickly, so we had better beware, for the most important take-home lesson from all human encounters with the powers of nature is simple—nature always wins.

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Attacking the Supply Lines: HIV-1 Restricts Alanine Uptake to Prevent T Cell Activation

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HIV commonly escapes host antiviral immunity by downregulating cell-surface immunoreceptors. In a recent issue of *Cell Host & Microbe*, Matheson et al. (2015) systematically examined how HIV-1 infection remodels the T cell surface and identified serine carriers SERINC3/5 and alanine transporter SNAT1 as targets of HIV-1 Nef and Vpu, respectively.

One of the hallmarks of HIV-1 infection is its ability to quietly spread throughout the host, often for extended periods of time, without raising major alarms within the immune system or causing overt signs of disease. The virus accomplishes this amazing feat in part by modifying the expression of numerous host proteins, particularly at the membrane of infected