Leprosy's drug resistance and origin revealed by genome analysis

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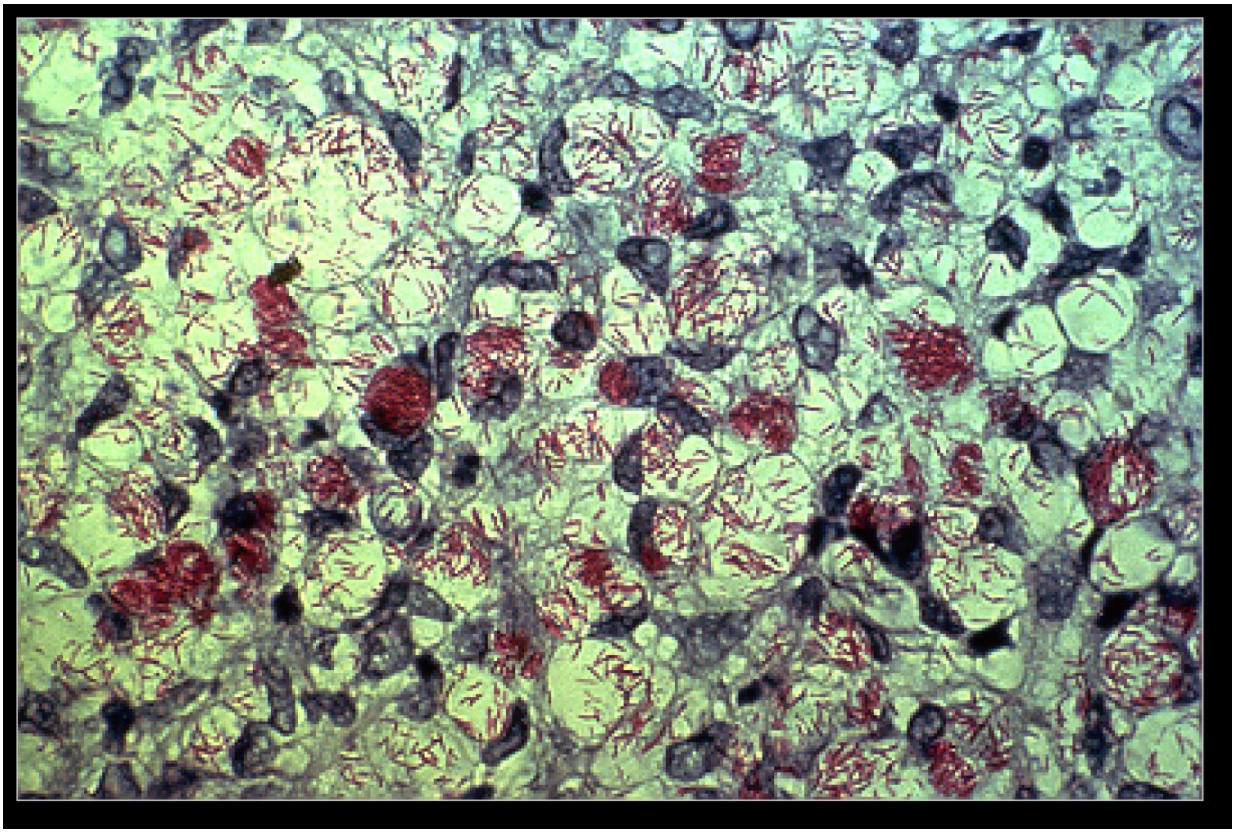

M. leprae, one of the causative agents of leprosy. Credit: Public Domain

Leprosy is an infectious disease with gruesome symptoms. It damages the skin, peripheral nerves, the upper respiratory tract, and the eyes. Despite being curable with multidrug therapy, leprosy still persists in

many developing countries, with more than 200,000 new cases every year and increasing drug-resistant strains of the leprosy bacterium, Mycobacterium leprae, emerging.

To fight leprosy, scientists need to better understand the biology of *M. leprae*, and specifically how it interacts with its host and resists antibiotics. However, studying the bacterium is difficult, as it cannot be grown in a lab.

Now, an international team of scientists led by Stewart Cole's lab at EPFL's Global Health Institute have isolated, sequenced and analyzed the genomes of 154 strains of *M. leprae* from around the world. The study found several genes that are associated with resistance to antibiotics, including new genes that might point to previously unknown mechanisms of drug resistance.

"This is an important finding," says Stewart Cole. "The way clofazimine, one of the main leprosy drugs, works is completely unknown but now we have a new lead to investigate thanks to this analysis of multidrug-resistant *M. leprae*."

Isolating *M. leprae* DNA was a challenging task, as the amount of bacteria in skin biopsies is generally low and varies greatly between patients. And after extracting the DNA, the researchers had to separate the bacterial DNA from the patient's. They did this with two techniques, one that increased the bacterium's DNA and one that decreased the patient's DNA. Once the bacterium's DNA was isolated, the researchers were able to sequence it and compare it with that from other samples.

The scientists also found eight strains of *M. leprae* whose genomes harbored an incredibly large number of random mutations, accumulated over a period of a few years or perhaps decades. These eight strains are all resistant to multi-drug therapy, and were the only ones in the study in

which a gene that is responsible for DNA repair is disrupted.

"It's a fascinating survival strategy against antibiotics," explains Andrej Benjak, the study's leading author. "Disrupting DNA repair will result in a storm of random mutations, increasing the chance that the right gene mutates at the right spot and lead to drug resistance. But random mutations can be deadly, so it's like a desperate, genetic Russian roulette for the bacterium."

The researchers also discovered that leprosy itself might have originated in the Far East. Several bacterial strains from East Asia belonged to the ancestral lineages of the leprosy bacilli. "People naturally assume that old human diseases originated in Africa, but for leprosy, the evidence points to Eurasia," says Charlotte Avanzi, one of the study's authors from Cole's lab.

Narrowing down the location of the origin will facilitate the reconstruction of the spread of the disease. "We need more samples from Central Asia and the Middle East, but these are hard to get due to current geopolitical issues," says Avanzi. "For Europe, where leprosy is eradicated, we have to rely on ancient human remains. But it's possible—we have developed the tools, and now we are ready to sequence even more samples."

More information: Andrej Benjak et al, Phylogenomics and antimicrobial resistance of the leprosy bacillus Mycobacterium leprae, *Nature Communications* (2018). DOI: 10.1038/s41467-017-02576-z

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