see if animals had been exchanged between past cultures. Data suggest that new domestic lineages of horse, including oriental bloodlines, were introduced to the south of mainland Europe between the 7th century (C7th) and the 9th century (C9th). During this period, a population shift in horses was also observed in Central Asia and Mongolia. Using population branch statistics along the genome of post-C7th–C9th Byzantine horses, compared with pre-C7th–C9th Gallo-Roman and Deer Stone horses, the authors asked if any traits were selected for by the C7th–C9th transition. Indeed, functional gene categories relating to cervical and thoracic vertebrae were over-represented in Byzantine horses, as was the speed-associated gene *MSTN*. Further data indicated that several genes associated with speed have been increasingly selected for in the past millennium.

Although domestic and Przewalski's horses are the only surviving horse lineages, the extinct horse species *Equus lenensis* was previously identified from three bones. As one of their equine subfossil samples from Southern Siberia was reminiscent of the *E. lenensis* lineage, but carried mitochondrial DNA that is specific to the New Siberian Islands and absent from the three bones, the authors propose that a novel 'ghost lineage' contributed to the genetic ancestry of this sample. Furthermore, the authors found that native Iberian horses from the 3rd and early 2nd millennium before common era cluster separately from *E. lenensis*, Przewalski's and the domestic horse lineage, indicating that a fourth lineage of horses existed early in domestication. However, although it has been suggested that Iberia could be a centre for horse domestication, data indicate that native Iberian horses are not a major genetic source of modern domestic horses.

This DNA time series sheds light on the complexity of horse evolution and is a resource for further analysing ancient horse genomes.

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ORIGINAL ARTICLE Fages, A. et al. Tracking five millennia of horse management with extensive ancient genome time series. *Cell* https://doi.org/10.1016/j.cell.2019.03.049 (2019)

metabolic information for the conditions being screened, which the authors call a 'white-box' machine learning approach.

As this machine-learning strategy yields pathway mechanisms, the investigators quantified the relative contributions of different metabolic pathways to the lethality profiles of each antibiotic. Consistent with the known stress that each of these antibiotics exerts on central carbon metabolism, the tricarboxylic acid (TCA) cycle scored highly as a determinant of toxicity for each of the antibiotics, thus validating the approach.

Shedding light on less-well-characterized mechanisms of antibiotic sensitivity, the team identified the early stages of purine biosynthesis as increasing sensitivity to AMP and CIP but decreasing sensitivity to GENT, which probably reflects the different cellular process targeted by the drugs. These effects were validated through various means: supplementation with purine biosynthesis metabolites, or genetic mutation or pharmacological inhibition of purine biosynthesis enzymes had the expected differential effects on GENT versus AMP and CIP lethality. Further metabolic simulations resulted in additional mechanistic predictions, which validated experimentally and led to an overall model whereby antibiotic stress triggers adenine limitation, purine biosynthesis, ATP demand, central carbon metabolism and respiration.

It will be interesting to determine whether nucleotide analogues have clinical value in potentiating antibiotic actions, as well as whether this overall network-based white-box strategy can provide useful insights into other aspects of bacterial pathology or for optimizing biotechnology applications. Although the study relied on a genome-scale model of bacterial metabolism, the authors highlight potential applications in human precision medicine, such as in understanding metabolic mechanisms of action of cancer drugs.

Darren J. Burgess

ORIGINAL ARTICLE Yang, J. H. A white-box machine learning approach for revealing antibiotic mechanisms of action. *Cell* https://doi.org/10.1016/j.cell.2019.04.016 (2019)

POPULATION GENETICS

Evolution to the rescue

Gulf killifish (*Fundulus grandis*) live in the Houston Ship Channel (Texas, USA) despite its heavy pollution from decades of industrial activity. A study in *Science* uses experimental and population genomic approaches to examine the molecular underpinnings of evolved pollution resistance in *F. grandis* by sampling populations across a pollution gradient. The findings pinpoint genetic variants introgressed recently from the geographically distant Atlantic killifish (*Fundulus heteroclitus*) that provide a large adaptive advantage.

Oziolor et al. obtained fish from 12 sites along the Channel spanning the pollution gradient, from clean to extremely polluted waters. Resistance to pollution was determined by the rates of occurrence of cardiac deformities in developing embryos exposed to a range of concentrations of a model halogenated aromatic hydrocarbon (HAH). Population variation in sensitivity to HAH-induced cardiac teratogenesis correlated with the level of habitat pollution, such that populations from the most polluted sites were resistant to HAH concentrations 1,000-fold higher than normal teratogenic levels.

Crosses between sensitive and resistant populations showed that resistance is intermediate in hybrid offspring, suggesting a genetic basis for the resistance phenotype. Resistance negatively correlated with activation of the aryl hydrocarbon receptor (AHR) pathway — the experimental knockdown of which had been shown previously to protect against HAH-induced cardiac teratogenesis — and desensitization of the AHR pathway correlated with pollution levels. Taken together, these findings suggest that desensitization to HAH-induced AHR signalling underlies resistance to pollution in *F. grandis*.

To determine the genetic basis of the resistance phenotype, the team sequenced whole genomes from fish that were either resistant, intermediate or sensitive to pollution. Genes encoding AHR signalling regulators showed the strongest signatures of selection. Moreover, resistant fish genomes exhibited signs of a recent population decline, for example, reduced nucleotide diversity compared with sensitive fish. This decline combined with the observed evolved resistance in the presence of strong recent selection "is consistent with evolutionary rescue in polluted populations", write the authors.

Whole-genome sequence comparison of *F. grandis* and Atlantic killifish (*F. heteroclitus*), some of which have also evolved pollution resistance, revealed evidence of recent adaptive introgression. This finding suggests that Atlantic killifish acted as the source of genetic variation enabling the evolutionary rescue of *F. grandis* populations from human-led environmental change. Given that the nearest *F. heteroclitus* populations reside >2,500 km away, making human-mediated transport the probable mechanism of introduction, this study highlights the benefit of unfragmented landscapes (allowing free movement of animals and thus genetic variation) for preserving biodiversity.

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ORIGINAL ARTICLE Oziolor, E. M. et al. Adaptive introgression enables evolutionary rescue from extreme environmental pollution. *Science* **364**, 455–457 (2019)