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The evolutionary history of wild and domestic brown rats (*Rattus norvegicus*)

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Teaser

A review of recent advances in our understanding of the evolutionary history of the brown rat and its association with humans

Abstract

The brown rat (*Rattus norvegicus*) occupies nearly every terrestrial habitat with a human presence and is one of our most important model organisms. Despite their prevalence, gaps remain in understanding the evolution of brown rat commensalism, their dispersal around the world, and mechanisms underlying contemporary adaptations to diverse environments. In this Review, we explore recent advances in the evolutionary history of brown rats and discuss key challenges, including finding and accurately dating historical specimens, disentangling histories of multiple domestication events, and synthesizing functional variation in wild rat populations with the development of laboratory strains. Advances in zooarchaeology and population genomics will usher in a new Golden Age of research on the evolutionary biology of brown rats, with positive feedbacks on their use as biomedical models.

Introduction

The rise of modern humans and our subsequent dispersal out of Africa to nearly every terrestrial habitat on Earth has profoundly altered the trajectory of life. No other animal has exerted such dominance over Earth's ecosystems (*1*). However, human construction of new agricultural and urban niches has facilitated the success of other mammals that are now nearly as, if not more, widespread and abundant as people.

Not surprisingly, many of these cosmopolitan mammals are rodents. Rodentia is the most speciose of all mammal orders, currently comprising 35 families and 2,680 extant species (*2*) with a dazzling array of morphological and ecological diversification. Three rodents in the family Muridae, the house mouse (*Mus musculus*), black rat (*Rattus rattus*), and brown rat (*Rattus norvegicus*) evolved a particularly close association with humans. These species are currently so abundant in human settlements that accurately estimating their population sizes or biomass is effectively impossible (*3*), even within individual cities (*4*). The brown rat was the last to spread worldwide, but is now globally distributed with humans. Their association with humans goes even deeper - domesticated brown rats are the second-most commonly used mammalian model organism (after *Mus musculus domesticus*), with labs in the USA alone housing hundreds of thousands of rats in any given year (*5*), providing inestimable contributions to basic and translational research.

Despite the importance of brown rats as pests and model organisms, relatively little attention has been paid to their ecology and evolution in the wild. This research gap is particularly surprising given that wild brown rats are major carriers of pathogens of human concern (*6*, *7*). Information on wild populations is crucial for pest management and urban ecology, but also for identifying biological variation in wild populations that may be absent from captive strains. A major exception was the Golden Age of wild rat research in the mid-twentieth century, primarily driven by Davis (*8*) and Calhoun (*9*) in the USA and Barnett (*10*) in the UK. Their extensive field and lab studies greatly improved our understanding of the socioecology and behavior of wild rats, and still provide the best information available for many aspects of rat biology. Scientific attention to wild rats then lagged for some time but has increased in recent years. New contributions from burgeoning fields such as population genomics and zooarchaeology augur a potential second Golden Age of wild rat research.

Uncovering the history of brown rats' association with humans, including identification of the timing and location of first association and adaptations for commensalism (Fig. 1), is increasingly within reach. Recent progress has elucidated the broad sweep of rat movements around the world (Fig. 2), but better estimates of dates and key locations of first arrival will be marked improvements. Whether rats serially adapted to new habitats, particularly given independent introductions to urban areas hundreds of times, remains an open question (Fig. 3). Similarly, the history of domestication both as pets and laboratory animals remains murky but rapid progress is possible. Genomic resources for rats were largely derived from inbred lab strains that represent only a small proportion of standing genetic variation in domesticated and wild lineages of rats. With renewed attention, uncovering the diversity of this cosmopolitan

species could greatly improve its utility as a biological model. In this review, we examine recent advances in our understanding of *R. norvegicus'* history with humans, and the ecological and evolutionary consequences of our close association with brown rats as both a wild, free-living animal and a captive species bred for research or companionship.

Evolutionary history of wild *Rattus norvegicus*

Rattus norvegicus is part of an old-world rodent clade (Family Muridae, subfamily Murinae) comprising nearly 10% of extant mammal species. *Rattus norvegicus* last shared a common ancestor with *M. musculus* ~10-11 mya and with *R. rattus* ~2-3 mya (*11*). The genus *Rattus* originated in southeast Asia in the last few million years and quickly spread throughout Asia and south into Australia and Melanesia. *R. norvegicus* is something of an outlier among *Rattus* given that its evolutionary origins and pre-commensal range may have been in colder climates than other rats. Currently, the oldest putative brown rat fossils date to the early Pleistocene in southern China, with northern Chinese and Japanese fossils dating to the late Pleistocene (Fig. 2) (*12*, *13*). Their distribution in east Asia over the last several 100k years likely depended on glacial cycles, with interglacial range shifts northward followed by subsequent southern dispersal. The brown rats' original habitat is unclear as nearly all extant populations are associated with humans, but they may have burrowed near grassland water courses. Brown rats are relatively cold hardy but must drink water often to survive long-term, and thus would not typically have been found far from water in arid lands. Unfortunately, the fossil record of this species remains quite poor and even existing specimens may belong to other species (*14*).

The Latin name *Rattus* (originally *Mus*) *norvegicus* (Berkenhout 1769) has roots in Dutch naturalist Albertus Seba's (1735) *Mus ex norvegia* (*15*) – possibly the earliest formal scientific description of the species. The common name of 'Norway Rat' – reflecting a misconception that rats arrived in the British Isles on ships from Norway, where they were not reported before 1762 (*16*) – was coined by 1731 and has remained in widespread usage, despite already being recognised as a misnomer by later 18th C naturalists. *Mus decumanus* (Pallas 1779) was the dominant name during the later 18th and 19th C.

Evolution of commensalism

Definitive answers to when and where rats became commensal with humans have proven elusive. One would need to establish where rats first co-occurred with humans, and then when rats became sufficiently reliant on human resources to cross an "anthrodependence" threshold (*17*). Population genetic data provide some evidence for the original range of this species. Both mitochondrial DNA haplotype diversity (*18*) and nuclear genome-wide estimates of heterozygosity (*19*) indicate that the greatest genetic diversity of brown rats is found in China, which supports this region as the likely center of origin. Northeastern China and SE Siberia have long been described as the original range of the species (*20*). In contemporary China, brown rats are typically more common at higher latitudes with colder climates, with the exception of burgeoning urban populations (*20*). Furthermore, demographic modeling of whole-

genome data indicates that brown rats did not spread into southeast Asia until the last millennium (*19*). An independent coalescent modeling effort concluded that brown rats originated in southern China and then spread to the north (*21*), although its phylogenetic tree topologies and other evidence also support northern China as the most ancestral population.

Recent theoretical proposals and empirical findings from other commensal taxa provide good starting points for understanding brown rat commensalism. The gradual emergence of human sedentism and plant cultivation in the late Pleistocene / early Holocene, accompanied by human population growth and increasingly dense settlements, likely supported large rodent populations (*22*). In China, such sedentary villages date back to at least 9000 BP (*23*), allowing considerable time for brown rats to evolve commensalism with humans. Rats likely initially used human resources opportunistically and then evolved to become more anthrodependent as agriculture developed, bringing with it larger-scale food storage and more extensive, permanent settlements (Fig. 1). The increasing prevalence of commensal house mice over time in the Levant (*24*) and genomic analyses of house sparrows (*25*) support such a scenario, with subsequent effects on other trophic levels such as predatory wild cats (*26*) . Better genomic datasets and modeling, but especially new identifications of zooarchaeological rat remains, are needed to robustly identify the original wild and commensal rat populations. Brown rat finds from Chinese Neolithic villages are mentioned in the literature (*14*) but are yet to be fully documented, while brown rats are found in association with human settlements in Japan from at least the Yayoi period (c. 2250-1700 BP) and perhaps sporadically earlier (*27*). Comparing ancient vs. contemporary skeletons and genomes could reveal adaptations to greater dependence on cultivated human food.

Human-assisted dispersal of brown rats around the world

Written historical records of the earliest rat migrations with humans are nonexistent or remain undiscovered, but population genomic analyses have revealed some broad outlines. Evolutionary clustering analysis of genome-wide SNP genotypes identified several distinct lineages of brown rats: east Asia, southeast Asia, central / northern Europe, and a western European group that is also widespread in the Americas, Africa, Australia and various islands (*28*). These lineages represent stepwise founder effects as rats moved out of Asia to the rest of the world, with a major expansion dating to the height of European imperialism. Complex patterns on the west coast of North America and New Zealand may result from multiple introductions from different source populations. Major demographic expansions may also be evidence of spread following evolution of a successful commensal habit in brown rats. Genomic estimates of effective population size indicate population contractions from 150 kya to 50 kya, followed by much more recent expansion with humans (*19*). Dating of population divergence events indicate spread into southeast Asia around 865 ya, and then into western Asia less than 100 years later. It is likely that brown rats were highly commensal by this time, so these dates may be considered as latest dates of the evolutionary origin of commensalism. Future improvements in dating and tracking these dispersal routes will come from additional whole genome sequences from poorly sampled regions (Figure 4), historical / ancient samples that yield usable DNA, and advances in population genomic modeling.

The brown rat's arrival in Europe is highly significant given the presumed role of European colonial shipping in its onward dispersal to the rest of the world. Various possible routes – not mutually exclusive – have been suggested. The dominant narrative of direct overland spread through Central Asia and Russia is not supported by Russian sources, which report that rats reached the Urals *from the west* in the late 19th or early 20th C (*29*). A more southerly route through the Iranian plateau and Caucasus is consistent with both phylogeographic data (*19*) and some 18th C sources e.g. (*30*), while there is little evidence for or against dispersal via the Mediterranean.

Early confirmed dates from Western Europe lend some support to the hypothesis of direct maritime spread from southern Asia to Western Europe. Europe boasts a relative wealth of written records of early rat presence that could be used to date their spread, but identifying biological species in historical sources is non-trivial. The emergence in 18th C Europe of modern systematics created both temporal and geographical biases: early reports might not be confidently identifiable as *R. norvegicus,* while verifiable descriptions inevitably cluster in areas studied by European-trained naturalists. Dates of reported rat presence in southern Russia and northern Persia, for example, say more about the late 18th-C expeditions of the St. Petersburg Academy of Sciences than about the timing of rat dispersal. Common dates and tropes repeated in recent texts are often highly speculative and/or based on sources written decades later. The date of 1716 for Copenhagen – associated with the Russian Imperial fleet's visit – derives from a rumor reported by Urne, governor on the island of Bornholm in 1755 (*31*). The story of rats crossing the Volga at Astrakhan in 1727 – often framed as an invasion of Europe – was first reported in 1779 by Pallas (born 1741) and actually describes an alleged eastward migration (*30*). The date of 1722 for Dublin given by Rutty (*32*) is perhaps more confident since he moved to the city in 1724, and early presence in Ireland is also supported by early 1730s newspaper reports mentioning a recently arrived and especially troublesome rodent under the name of 'Norway rat'. More conservatively, publication dates of credible reports provide *termini ante quos* for presence.

Archaeological evidence can fill in gaps, but published records must be treated with caution. Black and brown rats are often difficult to distinguish from fragmentary skeletal remains, especially juvenile individuals. Contemporary black rats typically have a more slender body and larger eyes and ears than brown rats, and a tail that is longer than the rest of their body. Geometric morphometrics on molar teeth can discriminate between various *Rattus* species (*33*) (CITATION) while collagen fingerprinting (ZooMS) can confidently distinguish black and brown rats even from fragmentary postcranial elements (*34*), overcoming limitations with morphological identification, but has yet to be applied widely. More problematically, rats may burrow into earlier archaeological layers and be assigned erroneously early dates. Specimens from secure contexts such as shipwrecks with known dates are thus particularly valuable, having demonstrably gone down with the ship. The earliest such find from Europe currently confirmed as *R. norvegicus*, however -- from a 1796 wreck off Corsica -- postdates written evidence for western Europe (*35*). Other finds, such as those reported from 14th C Italy (*36*) require direct radiocarbon dating, although technical limitations linked to fluctuating atmospheric ^{14}C effectively prevent this for specimens post-dating c.1650 (*37*) and potential consumption of

aquatic foods by rats complicates dating further due to offsets in ^{14}C between aquatic and terrestrial systems (i.e. 'reservoir effects').

Introduction and establishment of brown rats in North America has commonly been claimed to date to the American Revolution, with human-assisted dispersal to all parts of the continent by 1926 (*38*). A recent landmark paper (*34*) used ZooMS to identify rat remains to species from several archaeological sites and shipwrecks to further elucidate the "ratting of North America". The earliest confirmed brown rat in North America now dates to 1760 from the wreck of *Le Machault*, which traveled between France and West Africa starting in 1758 before sailing to North America and being destroyed in New Brunswick at the Battle of the Restigouche. Rat specimens from onshore sites may push back earliest arrival by a few decades, but their dating is less certain. Black rats declined precipitously over just a few decades beginning in the mid-18th century, strongly suggesting competitive displacement by brown rats (*34*). Stable isotope analyses revealed that brown rats in North America typically consumed greater amounts of animal protein than black rats, including when the species occur sympatrically. Greater competitive access to and/or behavioral preferences for meat may mostly explain the advantage of brown over black rats in commensal contexts.

Evolutionary history of domestication

Domesticated rats are most well-known as laboratory animals, but their domestication history is complex and encompasses multiple human motivations (Fig. 1). A recent historical perspective identified three major routes to domestication, with scientific use occurring most recently (*14*). Breeding of rats as companion animals with interesting color patterns can be confirmed as long ago as the mid-17th century in Japan and potentially China. Detailed breeding manuals for pet rats, or "fancy rats", date to the late 1700's in Japan and include descriptions of many pelage phenotypes present in contemporary fancy rats. Unfortunately, these original fancy lineages no longer exist as far as we know and would probably not have left Japan during this period of political isolation. Rats were bred in England and France in the early 1800's (and later in North America) to supply a blood sport known as "rat baiting", where people would wager on how many rats could be killed in a period of time by dogs placed in a small arena. Fancy rats also arose from selection of rats from rat baiting operations and later by rat catchers in mid-1800s Victorian England. The latter included the Royal Rat Catcher Jack Black, who bred and sold Albino, Black, Fawn, Grey, and Marked animals (*39*). These breeding efforts produced desirable color morphs such as albinos that were sold as pets and then later used in early scientific research in Europe. Some accounts indicate that albino and melanistic morphs were wild-living in English cities (*14*) – cycles of adaptation to captive breeding followed by release into the wild and feralization may have been a feature of early domestication in Europe. It is likely that these captive rat populations are the source of most of our contemporary lab strains.

North America became the site of intense breeding and use of rats for scientific research in the 1890s, with the neurologist Henry Donaldson playing a crucial role in developing rats for laboratory science. He wrote at length about the suitability of albino rats as lab animals because

their food preferences and neurological development were broadly similar to humans (*40*) . Donaldson brought four pairs of albino rats to the Wistar Institute at the University of Pennsylvania in 1906 to found captive populations that produced hundreds of scientific publications and many descendant strains of lab rats in the ensuing years. For example, Helen Dean King founded inbred strains at Wistar in 1909 that reached 38 generations of brother-sister matings by 1920. One strain ultimately reached 135 generations (*41*). Several major strains still in use today were derived directly from Wistar outbred lines, and many others have at least some Wistar ancestry. King also produced the “Brown Norway” strain from wild-living commensal rats caught in Philadelphia. While Wistar played an outsized role in generating lab rat strains, several others were developed elsewhere in North America and Europe. The genetic relationships between strains are now quite muddled, as repeated bottlenecks, inbreeding, and undocumented exchange of rats between colonies (or crossing with wild commensal rats) has obscured much of the evolutionary signal. Phylogenetic analyses have produced widely variable tree topologies due to variation in rat populations included in the analysis and genetic markers used. A full reconstruction of the history of lab rat strains is likely impossible; rats putatively of the same strain may show marked genetic structure across commercial vendors, breeding facilities, or even different rooms at the same breeding facility due to genetic drift and inbreeding (*42*). Analysis of mitochondrial genomes indicated that lab strains represent only a very small proportion of global genetic variation, although major strains such as Sprague-Dawley, Wistar, and Brown Norway represent different mitochondrial clades that diverged thousands of years ago (*43*). A broader effort to generate high-coverage whole genome sequencing is needed to improve our understanding of domestic lab strains and the amount of potential functional variation that they represent compared to wild populations.

Domesticated rats were favored lab animals for decades until the house mouse became more popular due to advances in creating transgenic mice in the 1980s. Nevertheless, interest in lab rat research was renewed in the late 1990s due to concerted efforts resulting in physiological screens for strain-dependent phenotypes, development of more efficient rat transgenic approaches, and sequencing of the inbred BN rat genome (*44*). Subsequent sequencing of multiple inbred strains led to establishment of the Rat Genome Database, a searchable repository of rat genome sequences and associated genetic variants with linkage to data from physiological screens (*45*). To mirror in part genetic diversity observed in outbred lab strains, the outbred National Institutes of Health heterogeneous stock (NIH-HS) was established from eight inbred strains. By combining whole genome sequencing of resulting stock lines, high accuracy SNP imputation, and well-defined haplotypes, investigators optimistically searched for causal variants at putative quantitative trait loci (QTL) (*46*). However, causal variants with major effects were rarely identified. In retrospect, the limited success of this approach is not surprising since the number and size of shared haplotypes in heterogeneous rat (and mouse) stocks remain quite large and thus so does the number of candidate variants. For strain-dependent phenotypes driven by single causal variants with major effects, consomic and congenic rat strains offer an alternative resource that also leverages genetic diversity between lab strains and chromosomal recombination to identify candidate variants (*47*). Newly available, deeply sequenced and annotated rat genome assemblies mRatBN7.2 (*48*) and now GRCr8 should

facilitate discovery of candidate genetic variants that influence environmental adaptation in lab rats and their wild relatives.

Environmental adaptation of introduced brown rats

Brown rats can survive in ecological contexts ranging from agricultural areas to remote islands, but temperate urban areas are where rats are consistently successful. The key to their success in cities is flexibility - brown rats consume nearly any food that humans eat and use a wide variety of terrestrial and subterranean infrastructure as harborage in addition to burrowing in open soil (*49*). Daily movements and dispersal distances for brown rats are generally short but highly variable; while rat movement may be restricted by roads, they can travel several km and use infrastructure such as sewer tunnels as corridors (*50*). This flexible behavior results in large rat populations living with humans in urban areas (*4*), resulting in zoonotic disease risks that are currently underappreciated (*6*, *7*). The rapid spread of brown rats into diverse habitats presents potentially powerful opportunities for the study of environmental adaptation (Fig. 3). Brown rats introduced to remote islands vs cities offer a clear ecological contrast, but even cities differ along many environmental axes that may drive evolutionary differences between populations. The most well-known example of adaptation in wild rats is directly related to human selection pressure: anticoagulant rodenticide resistance. Nonsynonymous mutations in VKORC1, the gene encoding vitamin K epoxide reductase, contribute to warfarin resistance and have been documented globally (*51*). In contrast, adaptation to environmental conditions in wild rats has been less widely studied. Genome scans of urban brown rats from New York City and China suggest that metabolism, response to diet, nervous system, and locomotion phenotypes may be under selection (*52*). The functional importance of these genomic signatures has not been established, but such scans indicate hypotheses for future work in domestic and wild populations. Time series cranial shape data in NYC rats also provide evidence of directional selection (*53*) for longer noses and shorter upper tooth rows, which are traits associated with adaptation to colder environments and higher quality diets that require less chewing. The heritability of these changes has not been established, but such rapid cranial shape change is common in rodents introduced to new environments (*54*). Studies of adaptation in introduced populations may be complicated by demography, e.g. founder effects in island populations (*55*), but population genomic approaches hold promise. Studies of wild populations across latitudinal and altitudinal gradients, as in house mice (*56*), could help identify candidate genes and phenotypes that facilitated expansion into diverse climatic niches. The rapid increase in available whole genome sequences produced from wild rats is a crucial resource for these studies that will only continue to grow in importance (Fig. 4).

Over the past century, laboratory rat strains have made innumerable contributions to our understanding of physiology, metabolism, and behavior (*57*). Bringing together the rich history of research in laboratory strains with data from wild populations may advance both biomedical and evolutionary research. Wild populations are a largely untapped reservoir of genetic variation and population genomic analyses may point to promising candidates underlying variation in phenotypes of broad interest. For instance, metabolism and response to diet, adaptive phenotypes suggested by genome scans in urban rats (*52*), are major areas of focus for human

health (Fig. 3). Research in lab strains can also spur insights for wild populations by helping to connect genetic variation in the wild to adaptive phenotypes. For example, hypoxia resistance is of broad physiological and evolutionary interest (*58*) (Fig. 3). Genetic variants in the Hypoxia Inducible Factor (HIF) signaling pathway, predominantly HIF-2 alpha (HIF2a)/Epas1 and Phd2/Egln1, likely contribute to high altitude adaptation in several vertebrates including humans (*59*). Altered levels or activities of HIF1a and HIF2a may contribute to hypoxia resistance in naked mole rats, which reside in sealed burrows for prolonged periods and hence may be exposed to severe intermittent hypoxic and hypercapnic conditions (*60*). However, the multitude of nonsynonymous changes in conserved residues of HIF1a, HIF2a, and other factors relating to hypoxia resistance (*61*), combined with the difficulties of genome engineering in the naked mole rat, are hurdles to exploring specific causative genetic variants. Wild brown rats form large colonies in underground burrows linked by extensive tunnels, which can be located in riverbanks, refuse dumps, or open expanses (*8*). Data on oxygen and carbon dioxide levels is minimal (*62*), but rats likely experience intermittent hypoxia and hypercapnia levels in densely occupied burrows. Research on high altitude adaptation or hypoxia resistance in wild brown rat populations is also lacking, but evidence for genetic variants that impact oxygen and carbon dioxide sensing come from strain-dependent physiological responses to hypoxia or hypercapnia (*63*). A major advantage of working with laboratory strains of the brown rat is that candidate variants could more tractably be evaluated via genome engineering coupled with detailed phenotyping. The deep body of research from laboratory strains may yield additional insights into phenotypes important to adaptation, including behavioral traits (*57*), which have been challenging to study in wild populations.

Conclusion

Progress over the last decade from population genomic and zooarchaeological efforts have revealed broad outlines of the intermingled story of brown rats and humans. Molecular confirmation of specimens from shipwrecks has produced high-confidence estimates of the latest arrival of brown rats in North America (*34*), indicating a high likelihood of success for similar efforts in Europe and elsewhere in the near future. Understanding the timing and geographical origins of commensalism in Asia is also within reach if specimens from the appropriate contexts can be documented and definitively dated. The next decade will likely see thousands of high-quality whole genomes sequenced from ancient and contemporary wild rats, as well as lab strains (Fig. 4). These genomic resources coupled with analytical advances should vastly improve our understanding of the movement of brown rats around the world, adaptations to diverse environmental conditions (especially cities and other human-dominated contexts), and novel functional variation that will improve the utility of rats as biomedical models. The next Chinese zodiac year of the rat in 2032 may well find biomedical researchers and evolutionary biologists experiencing a new Golden Age of rat research.

Figures

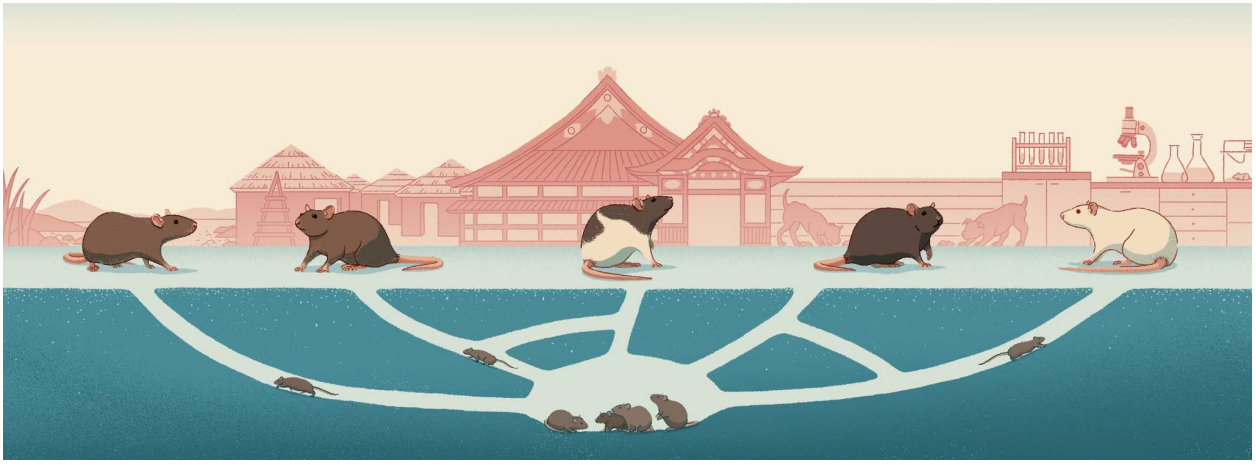

Fig. 1. Routes to the evolution of commensalism and domestication in the brown rat, *Rattus norvegicus*.

From left to right, this figure shows 1) a brown rat in its original wild habitat in eastern Asia, most likely near water courses in grassland areas; 2) a brown rat becoming increasingly commensal with humans in neolithic settlements in China; 3) a “fancy rat” with a “hooded” pelage pattern domesticated in Japan during the Edo period (early 17th century); 4) a rat bred for the blood sport knowns as “rat baiting” in the UK and France, some of which presented with melanistic or albino pelage characteristics; and 5) a typical laboratory rat bred for biological research, first in western Europe and then intensively in North America at the Wistar Institute in Philadelphia, PA and elsewhere. The burrow structure indicates that fancy rats in Japan were likely domesticated from wild-caught commensal rats, and that rats bred for rat baiting and other purposes were later used as the first lab rats. Illustration by Christina Chung.

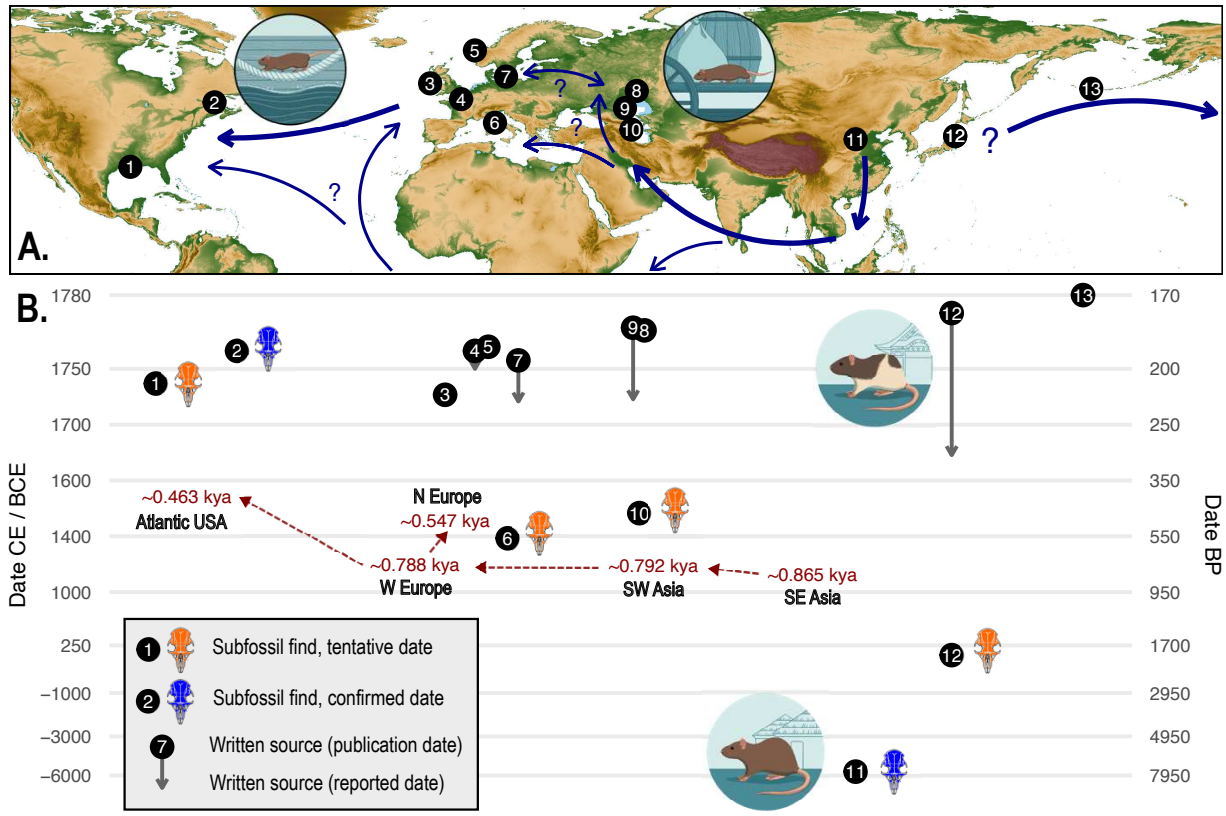

Fig. 2. Map (A) and timeline (B) showing selected archaeological, historical, and phylogenetic evidence for brown rat dispersal and early interaction with humans.

A. Locations of early evidence for human-associated brown rats and suggested dispersal routes (blue arrows; thicker lines represent more confident proposed routes). Key to locations: 1. New Orleans, 2. Le Machault shipwreck, 3. Dublin, 4. Paris, 5. Norway, 6. Tarquinia, 7. Bornholm, 8. Oral, 9. Astrakhan, 10. Baku, 11. Northern China, 12. Japan, 13. Aleutian islands (*14*, *27*, *30–32*, *34*, *36*, *64–66*). B. Types and dates of evidence at these locations (logarithmic scale based on years before 1800 CE). 'Confirmed' subfossil finds (blue skulls) are those with both identification and date considered secure. Written sources are placed conservatively at date of writing; grey downwards arrows point to dates claimed within sources. Red dates and arrows represent phylogenetically inferred divergence times from (*19*). Spot illustrations by Christina Chung.

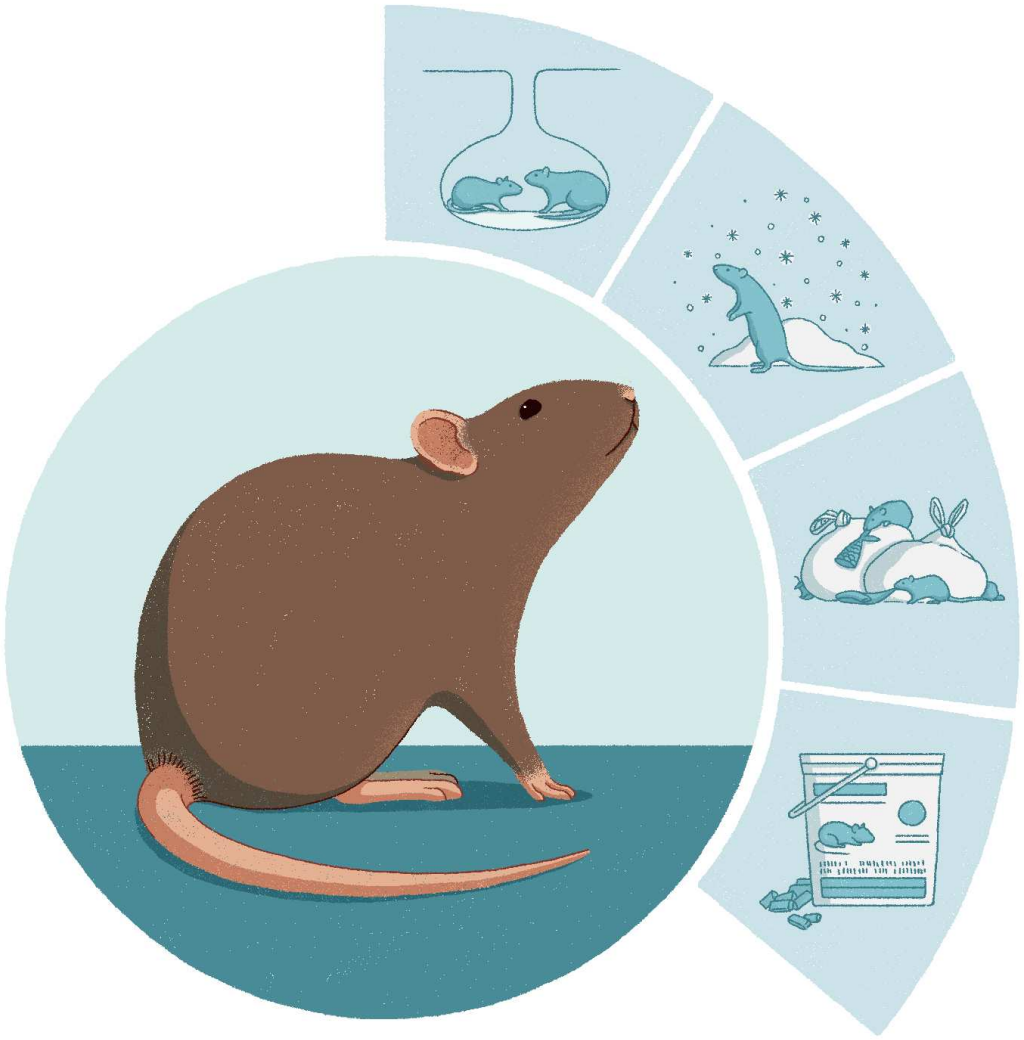

Fig. 3. Potential environmental selection pressures leading to adaptation in wild brown rats.

Brown rats occupy a broad variety of environmental conditions and are likely adapting to several selection pressures around the world. This figure highlights several potential selection pressures going clockwise from the top: 1) hypoxic or hypercapnic conditions in underground burrow systems (or at high elevation) may influence the evolution of respiratory / oxygen transport traits; 2) colder or more extreme climatic conditions than in their original native range may favor cold tolerance or other physiological phenotypes; 3) novel diets, particularly varying amounts and types of human foods around the world, may result in metabolic adaptations; and 4) constant exposure to anticoagulant rodenticides and other synthetic compounds designed for lethal control of their populations results in the evolution of rodenticide resistance. Illustration by Christina Chung.

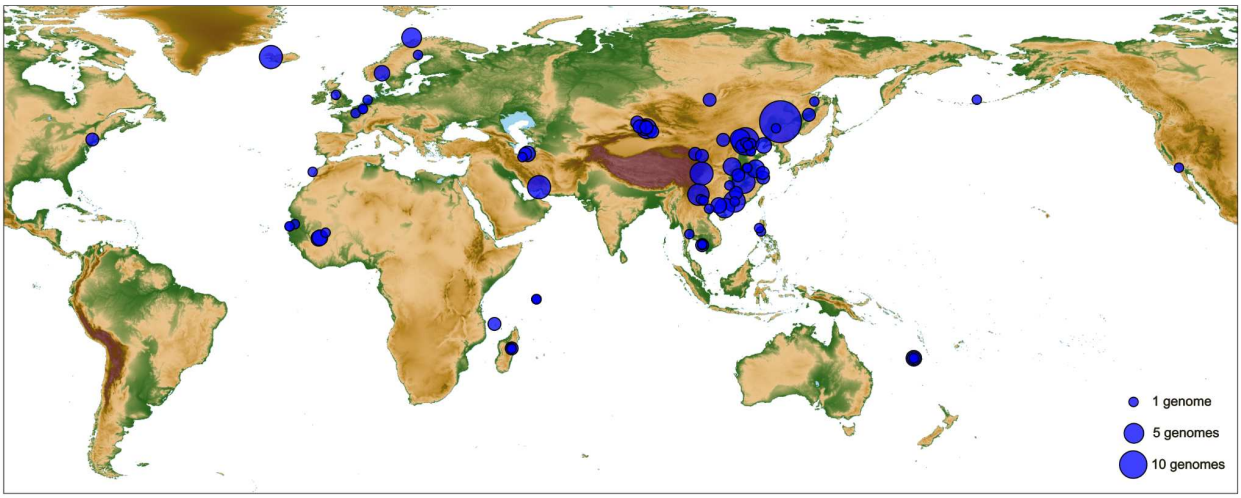

Fig. 4. Whole genome sequences available from wild brown rats around the world.

Recent renewed interest in the phylogeography and adaptive evolution of brown rats has led researchers to sequence over 200 whole genomes from wild brown rats. This map shows the geographic locations of sequenced rats as blue circles, with the size of the circle proportional to the number of genes (see map key). Many of these genomes are relatively low coverage (i.e. less than 5X coverage) and are biased towards east Asia, but coming years will likely bring a rapid increase in the number of high quality sequences available to rat researchers. These genomes will serve both basic evolutionary research and investigations of potentially useful functional variation in wild rats that can be explored in laboratory strains.

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