Current Biology
Magazine

Quick guide

African striped mice

Ricardo Mallarino[1],
Neville Pillay[2], Hopi E. Hoekstra[3],
and Carsten Schradin[2,4,*]

Figure 1. A striped mouse from the Succulent Karoo in South Africa.
The striped mouse population in the Goegap Nature Reserve of South Africa has been studied for 17 years, documenting several interesting behaviors including a flexible social organization. This species is now kept in several laboratories and used in different fields of research, such as animal behavior, evolutionary developmental biology, and chronobiology. (Photo by Claudia Menzel, field assistant at the striped mouse project in Goegap, South Africa.)

What are striped mice? The African striped mouse, *Rhabdomys pumilio*, also known as the four-striped grass mouse, occurs in southern Africa, where it inhabits shrublands, semi-deserts and even some urban areas (Figure 1). African striped mice are characterized not only by their eponymous dorsal-lateral stripes, but also by their social flexibility — in particular their capacity to switch between a solitary and social lifestyle — and diurnality, all of which are rare characteristics among muroid rodents. This unique combination of morphological and behavioral traits, along with their phylogenetic proximity to laboratory rodent models, make African striped mice an exciting species for both field and lab studies.

Why do striped mice have stripes? African striped mice have two pairs of parallel racing stripes that flank the midline of their dorsal coat in a light–dark–light arrangement. This periodic stripe pattern and its position along the dorso-ventral axis is remarkably conserved across individuals, in contrast to other striped mammals, such as tapirs, whose patterns change from juvenile to adult, or tigers and zebras, which have highly variable patterns that can be used to distinguish specific individuals. For other striped species, such as garter snakes, there is evidence that dorso-lateral stripes function in predator evasion, but so far no experiments have been done to test the function of the stripes in African striped mice (or other rodents). Because of the diurnal lifestyle and tendency to inhabit open environments of African striped mice, researchers have speculated that their stripes help camouflage these mice, minimizing attacks from their visually hunting predators, such as small-sized carnivores (mongooses or wild cats, for example) and birds of prey, although it should be noted that snakes are also a major predator of these mice.

How are stripes formed? A recent study, using a laboratory colony of African striped mice, asked which genes are involved in the development of their iconic stripes. During embryonic development in mammals, pigment cells (melanocytes) colonize hair follicles, and once mature, produce pigment, which is then deposited along the growing hair. When these mice are born, their stripes are already evident, indicating that the machinery for establishing stripe patterns operates during embryogenesis. Comparison of gene expression between light (with un-pigmented hairs) and dark (fully eumelanic hairs) stripes showed that the developmental gene *Alx3* (*ALX Homeobox 3*) was differentially expressed in the skin: high levels in the light stripes and low levels in dark ones. Further experimentation demonstrated that *Alx3* suppresses the maturation of melanocytes in a cell autonomous fashion. Thus, in the region expressing *Alx3*, melanocytes remained immature and could not produce pigments, leading to the formation of unpigmented hairs in the light stripes. This work in striped mice identified a new pigmentation gene and a new mechanism for pigment patterning, and also led to new research questions: what regulates *Alx3* and directs its spatial expression pattern? And, does *Alx3* play a role in stripe formation in other species, mammals and beyond? More generally, this study established African striped mice as an exciting model in evolutionary developmental biology and opened the door for exploring fascinating questions about the genetic and developmental mechanisms driving the tremendous diversity of pigment patterns observed in wild vertebrates.

Why is the social behavior of striped mice so special? Because they are diurnal, occupy open habitats, and are easily habituated to the presence of observers, we know more about the natural behavior of African striped mice than that of any other small rodent. A particularly intriguing aspect of African striped mice is their ability to switch between a social and a solitary lifestyle. Numerous studies have demonstrated the benefits of group-living in various taxa, mainly improved predator avoidance and foraging, and, particularly in small animals, thermoregulatory benefits of social huddling. In contrast, it has generally been assumed that solitary animals benefit from avoiding reproductive competition within groups, but the forces driving this lifestyle rarely have been measured. In the African striped mouse, long-term field studies demonstrated that the avoidance of reproductive competition is, indeed, the primary driver of a solitary lifestyle, which is preferred when free territories are available. Outside the breeding season, however, when no reproductive competition exists, striped mice are always social and engage in social huddling, a behavior that allows them to reduce thermoregulatory costs during the food restricted dry season. This temporal switch in sociality not only allows striped mice to adapt to rapid environmental change, but also offers scientists a unique opportunity to study the processes mediating group *versus* solitary living within a single species. Identifying the underlying mechanisms driving switches in social organization and how these evolve is an exciting opportunity that will engage researchers from various disciplines, from behavioral ecologists to neuroscientists.

African striped mice also show alternative reproductive tactics, with discrete reproductive behavioural phenotypes. Alternative reproductive tactics are common in males of many species, like satellite males in crickets and tree frogs or sneaker males in different fish species. What makes striped mice unusual is that *both* sexes have alternative reproductive tactics. Males can either defend groups of females or adopt a solitary sneaking tactic, referred to as roaming. Females can breed in communal groups or leave these groups and breed solitarily. If all females decide to breed solitarily, because population density is low and every female can inhabit a high quality territory, no female groups are available for males to defend, so all males become solitary roamers. Thus, social flexibility is driven by the female's choice of reproductive tactics. This is in contrast to species where only males follow alternative reproductive tactics and the social organisation of the population appears rigid.

Are striped mice a good laboratory model species? Yes! African striped mice can be maintained and bred in the laboratory under controlled conditions, under similar conditions to that for standard laboratory mice (*Mus musculus*). Striped mice have a gestation time of 23 days, breed all year-round, and display post-partum estrous, which allows one to accurately time pregnancies. Previously, captive colonies of African striped mice existed only in South Africa, but colonies have been recently established also in France, the U.S. and the U.K., which will make these mice available for many scientists of different disciplines. Moreover, because striped mice are closely related to the laboratory mouse and rat — striped mice diverged from *Mus* and *Rattus* approximately 5–6 million years ago; all three belong to the Muridae family — many of the molecular tools and antibodies are easily transferable. Finally, the draft genome has been completed recently, opening the door for understanding the detailed genetic and molecular mechanisms underlying its unique biological features.

What other research areas could benefit from studies in striped mice? African striped mice have a unique set of features that make them an attractive model species for tackling questions in a variety of disciplines, including developmental biology, comparative genomics, neurobiology, and behavioral ecology. Because striped mice are diurnal rodents that evolved from nocturnal ancestors, they are uniquely suited for understanding the physiological, genetic, and molecular mechanisms that contribute to this shift, for example, alterations in circadian rhythm. Moreover, striped mice have evolved a distinct retinal anatomy characterized by a thick inner plexiform layer and a cone-like organization of the outer segment layer, which indicates a high amount of retinal data processing relative to other muroid rodents. This heavy reliance on vision offers an exciting opportunity for comparative studies at a physiological and genomic level. Interestingly, striped mice — unlike laboratory mice and most mammals — have pigmented skin, that is, melanocytes are distributed in the dermis and epidermis rather than limited to only hair follicles, which may provide protection from UV damage. Since there are various human skin conditions affecting melanocyte behavior, such as vitiligo and melanoma, striped mice may be a relevant system in which to model these and gain insights into their etiology.

In addition to their well characterized social flexibility, striped mice display a number of additional fascinating behaviours. For example, since they evolved in a habitat with seasonal droughts, striped mice overfeed when fed *ad libitum*. Without a restricted diet, they quickly become obese in the lab, which appears linked to the level of leptin, a hormone that is secreted from the adipose tissue and known to suppress food intake. In laboratory mice, leptin secretion is correlated with adipose tissue mass. In striped mice, however, leptin levels are dissociated from adipose tissue mass, allowing these mice to gain weight when food is readily available while suppressing energetically costly foraging behavior when food is scarce. Moreover, striped mice also show abnormal repetitive behaviors in the lab, and thus represent a comparative model for understanding the development of psychological disorders.

Striped mice live in a seasonal habitat with dry seasons that can be mild or extreme, which is unpredictable. They are currently used as a model to understand how animals can cope with such change via physiological and behavioral flexibility. Thus, striped mice might also offer us insight into how individuals can cope with climate change — and when and why they cannot!

Finally, although striped mice have been classified as a single species, karyotypic and genetic evidence suggests that there are at least two species, *Rhabdomys pumilio* and *R. dilectus*, and more recent studies have even proposed four distinct species. *R. pumilio* and *R. dilectus* occupy different ecological niches and have at least two contact zones in South Africa, opening the door for studies on ecological speciation, that is, how divergent selection in different habitats may lead to the formation of new species.

Where can I learn more?

Dewsbury, D.A., and Dawson, W.W. (1979). African four-striped grass mouse (*Rhabdomys pumilio*), a diurnal-crepuscular muroid rodent, in the behavioral laboratory. Behav. Res. Meth. Instrument. *11*, 329–333.
Du Toit, N., Pillay, N., Ganem, G., and Relton, C. (2016). A conservation assessment of Rhabdomys spp. In The Red List of Mammals of South Africa, Swaziland and Lesotho, M. Child, L. Roxburgh, E. Do Linh San, D. Raimondo, and H. Davies-Mostert, eds. (South African National Biodiversity Institute and Endangered Wildlife Trust).
Hill, D.L., Pillay, N., and Schradin, C. (2015). Alternative reproductive tactics in female striped mice: heavier females are more likely to breed solitarily than communally. J. Anim. Ecol. *84*, 1497–1508.
Mallarino, R., Henegar, C., Mirasierra, M., Manceau, M., Schradin, C., Vallejo, M., Beronja, S., Barsh, G.S., and Hoekstra, H.E. (2016). Developmental mechanisms of stripe patterns in rodents. Nature *539*, 518–523.
Meynard, C.N., Pillay, N., Perrigault, M., Caminade, P., and Ganem, G. (2012). Evidence of environmental niche differentiation in the striped mouse (*Rhabdomys sp*.): inference from its current distribution in southern Africa. Ecol. Evol. *2*, 1008–1023.
Rambau, R.V., and Robinson, T.J. (2003). Molecular genetics *of Rhabdomys pumilio* subspecies boundaries: mtDNA phylogeography and karyotypic analysis by fluorescence in situ hybridization (FISH). Mol. Phyl. Evol. *28*, 564–575.
Rymer, T. L., Pillay, N., and Schradin, C. (2016). Resilience to droughts in mammals: A conceptual framework for estimating vulnerability of a single species. Q. Rev. Biol. *91*, 133–176.
Schradin, C., Lindholm, A.K., Johannesen, J., Schoepf, I., Yuen, C.-H., König, B., and Pillay, N. (2012). Social flexibility and social evolution in mammals: a case study of the African striped mouse (*Rhabdomys pumilio*). Mol. Ecol. *21*, 541–553.
Schradin, C. (2013). Intraspecific variation in social organization by genetic variation, developmental plasticity, social flexibility or entirely extrinsic factors. Philos. Trans. R. Soc. B. Apr 8; 368(1618), 20120346.
Schradin, C., Raynaud, J., Arrivé, M., and Blanc, S. (2014). Leptin levels in free ranging striped mice (*Rhabdomys pumilio*) increase when food decreases: the ecological leptin hypothesis. Gen. Comp. Endocrinol. *206*, 139–145.

[1]Department of Molecular Biology, Princeton University, Princeton, NJ 08540, USA. [2]School of Animal, Plant and Environmental Sciences, University of the Witwatersrand, South Africa. [3]Howard Hughes Medical Institute, Department of Organismic & Evolutionary Biology, Department of Molecular & Cellular Biology, Museum of Comparative Zoology, Harvard University, Cambridge, MA 02138, USA. [4]Université de Strasbourg, CNRS, IPHC UMR 7178, F-67000 Strasbourg, France.
*E-mail: carsten.schradin@iphc.cnrs.fr

Primer

Animal left–right asymmetry

Martin Blum* and Tim Ott

Symmetry is appealing, be it in architecture, art or facial expression, where symmetry is a key feature to finding someone attractive or not. Yet, asymmetries are widespread in nature, not as an erroneous deviation from the norm but as a way to adapt to the prevailing environmental conditions at a time. Asymmetries in many cases are actively selected for: they might well have increased the evolutionary fitness of a species. Even many single-celled organisms are built asymmetrically, such as the pear-shaped ciliate *Paramecium*, which may depend on its asymmetry to navigate towards the oxygen-richer surface of turbid waters, at least based on modeling. Everybody knows the lobster with its asymmetric pair of claws, the large crusher usually on the left and the smaller cutter on the right. Snail shells coil asymmetrically, as do the organs they house. Organ asymmetries are found throughout the animal kingdom, referring to asymmetric positioning, asymmetric morphology or both, with the vertebrate heart being an example for the latter. Functional asymmetries, such as that of the human brain with its localization of the language center in one hemisphere, add to the complexity of organ asymmetries and presumably played a decisive role for sociocultural evolution. The evolutionary origin of organ asymmetries may have been a longer than body length gut, which allows efficient retrieval of nutrients, and the need to stow a long gut in the body cavity in an orderly manner that ensures optimal functioning. Vertebrate organ asymmetries (*situs solitus*) are quite sophisticated: in humans, the apex of the asymmetrically built heart points to the left; the lung in turn, due to space restrictions, has fewer lobes on the left than on the right side (two versus three in humans), stomach and spleen are found on the left, the liver on the right, and small and large intestine coil in a chiral manner (Figure 1A). In very rare cases (1:10,000), the organ situs is inverted (*situs inversus*), while

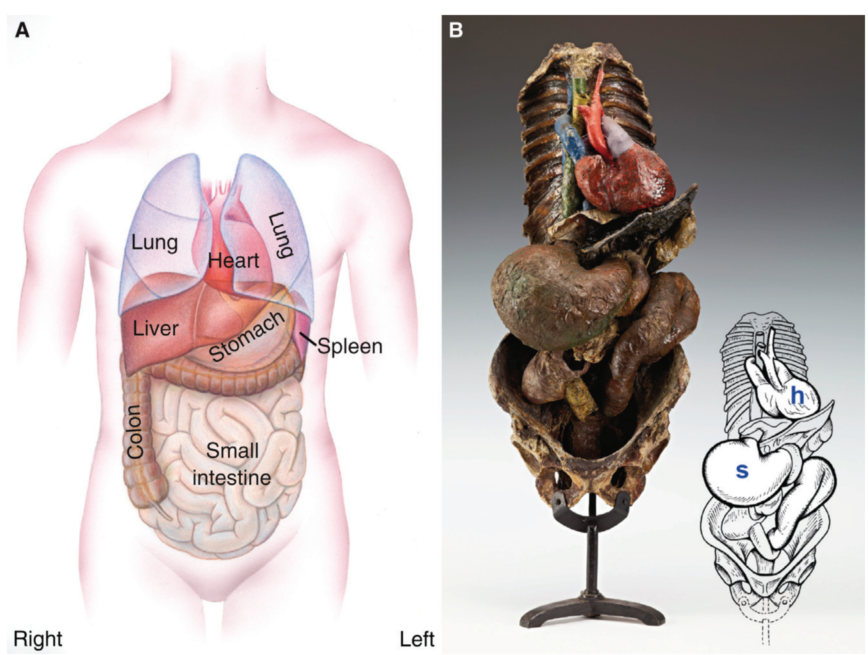

Figure 1. Human organ situs.
(A) Normal arrangement (*situs solitus*). (B) Historical preparation by Meckel the Elder of a human torso displaying heterotaxia, with normal position of the heart (h) and inverted stomach (s). From the Meckelsche Sammlungen of the Institute of Anatomy and Cell Biology, Martin-Luther University Halle-Wittenberg (Germany). Photograph by Janos Stekovics. Artwork by Bernd Schmid (University of Hohenheim).