

Emerging Model Organism

The Lesser Egyptian Jerboa, *Jaculus jaculus*: A Unique Rodent Model for Evolution and Development

Kimberly L. Cooper

Harvard Medical School, Department of Genetics, Boston, Massachusetts 02115

Tetrapods that have evolved the ability to run or bound at great speeds over long distances have repeatedly converged on specific morphological limb adaptations, including the loss of lateral digits, elongation of limb segments, and fusion of individual elements. Many of the more familiar cursorial animals, such as horses and deer, are large and do not lend themselves well to experimental embryonic analyses. However, a group of lesser-known bipedal rodents, the three-toed jerboas, has become an exceptional model for studying the developmental and molecular mechanisms shaping these limb morphologies. The lesser Egyptian jerboa, *Jaculus jaculus*, represents the most derived subfamily of jerboas and shows loss of the anterior and posterior hindlimb digits, fusion of the three central metatarsals, and dramatic elongation of the hindlimb relative to the forelimb with disproportionate elongation of the metatarsals. In addition, several unique physiological and morphological characteristics make these excellent animals for evolutionary studies. As small docile rodents, they are amenable to rearing in a laboratory setting and, along with several related species with a variety of skeletal morphologies, are plentiful enough in the wild to support field collections. The close evolutionary relationship to *Mus musculus* and the development of genomic resources for *J. jaculus* support comparative developmental and molecular analyses.



BACKGROUND

The jerboas comprise 33 species in the order Rodentia, superfamily Dipodoidae, family Dipodidae. The superfamily includes the nearest relatives of jerboas, the birch mice (Sicistidae) and jumping mice (Zapodinae), and is a sister taxon to the Muroidea, which includes hamsters, gerbils, true mice, and rats. The jerboas are further divided into four subfamilies—Euchoreutinae (the long-eared jerboa), Cardiocraniinae (the pygmy jerboa), Allactaginae (the four- and five-toed jerboas), and Dipodinae (the three-toed jerboas). The species *Jaculus jaculus* (the lesser Egyptian jerboa) (see Fig. 1) is in this latter and most derived subfamily of jerboas (Shenbrot et al. 2008).

The oldest fossilized jerboas were found in sediments from the early middle Miocene epoch in Gansu Province of China (Young 1927). The partially fused and elongated metatarsal cannon bone indicates the early acquisition of cursorial features. Elongation of the hindlimb and reduction of digit number has been hypothesized to be an adaptation for running bipedally at high speeds and over great distances in search of food in arid climates. In support of this hypothesis, an increased home-range distribution has been correlated with the length of the hindlimb (Rogovin 1999), and correlations between jump length and habitat show that the most proficient leapers are found in the most sparsely vegetated deserts (Berman 1985).

Correspondence: kcooper@genetics.med.harvard.edu

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Cite this article as *Cold Spring Harbor Protoc*; 2011; doi:10.1101/pdb.emo066704



FIGURE 1. Adult lesser Egyptian jerboa in mid hop. The greatly elongated hindlimbs are evident with particularly striking metatarsals and three toes on each hindfoot. The forelimbs are tucked under the chin, and the elongated tail is used as balance.

The worldwide distribution of extant jerboa species is extensive throughout the arid and desert regions of North Africa and Central Asia. Specifically, *J. jaculus* is found in North Africa, throughout the Arabian Peninsula, and as far north as Southwestern Iran. Although several species of jerboas have been designated as vulnerable or threatened by the International Union for Conservation of Nature (IUCN), *J. jaculus* is considered of “least concern” and is in fact sold as falconry food in several Arabian countries, including Jordan and Syria (Amori et al. 2008). The ecology and physiology of several species of jerboas have been studied for decades, but *J. jaculus* has only recently been established as a laboratory model system for developmental analyses by Dr. Kimberly Cooper and Dr. Cliff Tabin at Harvard Medical School.



SOURCES AND HUSBANDRY

Rodent enthusiasts and researchers have had difficulty breeding any species of jerboa in captivity because common methods of rearing rodents in open cages resulted in litters that were frequently abandoned and died without maternal care. The first marked success was in 2007 at the Breeding Centre for Endangered Arabian Wildlife (BCEAW) in Sharjah, UAE. It seems that successful breeding and rearing in captivity requires the presence of a hinged dual-chambered box with a low entrance that the animal can seal with bedding to create a secure and isolated burrow-like nest area (Jordan 2009). Husbandry methods have now been adapted to a laboratory setting (see **Husbandry and Breeding of the Lesser Egyptian Jerboa, *Jaculus jaculus*** [Jordan et al. 2011]).

The species of choice for breeding in captivity is the lesser Egyptian jerboa (*J. jaculus*) because it is among the smaller jerboas, weighing ~55 g, and it does not hibernate through the winter (Walker 1964). The founding animals for the BCEAW colony were shipped from Syria, initially intended as food for raptors, and a successful breeding program has since expanded the population. The founder animals for the Harvard University colony were caught in the wild and provided by an animal supplier located near Cairo, Egypt. Seventy adult animals were shipped in August 2009, and the first litter was born in April 2010. There has been a remarkably low level of adult mortality consistent with observations that *J. jaculus* can survive for 5–6 years in captivity (Weigl et al. 2005), and animals that are at least 2 yr old continue to produce litters. As this colony continues to expand, animals will be available to found additional research colonies, and specimens can be provided for specific needs.

Although some species are considered threatened or endangered, several species of five- and three-toed jerboas are prevalent in wild populations, where they are often viewed as agricultural pests. In

particular, we have captured animals in the Erdos desert region of Inner Mongolia, China and in the Fukang desert region of Xinjiang, China. These localities are both excellent sources of the small five-toed jerboa (*Allactaga elater*) and the northern three-toed jerboa (*Dipus sagitta*) and allow for animal observations in their native habitat. Moreover, the jerboa species geographically distributed throughout Central Asia and Northern China hibernate through the winter and breed within 1–2 wk of emerging from their burrow in the spring. Consequently, ~80% of female animals are pregnant when they are captured over the course of 6 wk from the end of hibernation, reducing the number of animals needed for an adequate embryo collection. Jerboas notoriously avoid standard live-animal traps, so we have relied on local knowledge and local assistance to spotlight at night in the desert and capture startled animals with fisherman's landing nets. The embryo collection is a valuable resource to complement the captive breeding colony as the colony continues to expand and methods for identifying timed pregnancies are established.

USE OF JERBOAS AS A MODEL SYSTEM

Because jerboas have only recently been adapted to a laboratory setting, much of the published work using these animals has focused on systematics and on physiology using wild-caught adult animals. Specifically, the greater Egyptian jerboa, *Jaculus orientalis*, which undergoes brief periods of overwinter hibernation, has been the subject of research on liver metabolism, skeletal muscle physiology, and neurochemistry during hibernation (Kabine et al. 1998; Soukri et al. 1996; Berrada et al. 2002; El Ouezzani et al. 2001). Two notable works have described the morphology of the foot and the acquisition of bipedality in young animals. Using embryos and juveniles collected during the breeding season of wild populations in Egypt, Dr. Adel Shahin identified the individual metatarsal condensations that ultimately fuse into the cannon bone of the foot in *J. jaculus*, *J. orientalis*, and *Allactaga tetradactyla* (Shahin 2005). Drs. Eilam and Shefer described the locomotion of one litter of juvenile *J. orientalis* born of animals caught in the desert of Israel (Eilam and Shefer 1997). Their work highlights the transitions from “creeping” on the forelimbs while dragging the hindlimbs to the side, to bringing the hindlimbs underneath the body into a quadrupedal walk, and finally emerging into a true upright stance. In the process of characterizing the acquisition of bipedality, they also describe key developmental milestones showing the fact that young jerboas develop rather slowly compared to other small rodents. However, to date, research on jerboa development has been geographically limited to these groups with local access to live specimens.

With the establishment of breeding protocols for *J. jaculus* to complement the extensive collection of embryos from wild-caught populations of *D. sagitta* from Northern China, we are now able to delve into a deeper understanding of the development of unique skeletal morphologies. As a near relative of one of the best-understood models for vertebrate limb development, the house mouse *M. musculus*, *J. jaculus* is an outstanding model for understanding developmental mechanisms of limb evolution. Furthermore, although the North American kangaroo rat has elongated the hindlimb skeleton to a lesser degree and convergently lost the first digit in some species, the three-toed jerboa represents the most extreme divergence from an ancestral “mouse-like” morphology. We are beginning to address the question of hindlimb digit reduction by investigating the differences in limb bud morphology and patterns of cell death and proliferation throughout early development that lead to the formation of only the three central toes. Subsequently, the hindlimb skeleton undergoes allometric elongation of the distal elements, most dramatically the metatarsals that are ultimately longer than the femur in the adult. We are characterizing the temporal dynamics of this elongation as well as various cellular contributors to long-bone growth. Also, although the three central metatarsals of the jerboa initially condense and ossify as individual elements, they fuse postnatally into a single cannon bone. Our ultimate goal is to understand the molecular mechanisms that give rise to each of these derived characteristics.

Initial interest in jerboa development and evolution focused on features of the hindlimb skeletal pattern, but an array of morphological and physiological modifications are attributed to an animal well adapted to its nocturnal desert environment and bipedal mobility. Derived features of the

skull include enlarged auditory bullae that are so phenomenally pronounced as to contribute to the naming of the species *Allactaga bullata*. The effect of enlarging the mastoid and bulla is to widen the overall dimensions of the posterior skull. The anterior portion of the jugal bone is also enlarged and comes into contact with the lacrymal forming a robust orbit for the greatly enlarged eye (Howell 1932). The dentition of the jerboas is of interest because of the presence of the fourth premolar in some species and morphology of the first molar that raise questions about the developmental relationship of these structures and give insight into the evolutionary relationships of Dipodoid and Muroid rodents (Rodrigues et al. 2011).

Several unique characteristics of the axial skeleton correlate with the evolutionary trend toward an upright posture. The posterior five cervical vertebrae are shortened and fused ventrally to form a rigid neck, a convergent characteristic shared by some species of jumping rodents (kangaroo rats and springhares) and cetaceans (dolphins and whales) (Reynolds 1897). Additionally, the anterior skeleton, including the forelimbs, thoracic vertebrae, and ribcage, is much smaller and more delicate than the lumbar vertebrae, pelvic girdle, and tail, having the effect of shifting the center of mass over the pelvis and thus bringing the jerboa upright. In fact, the jerboa has only 12 thoracic vertebrae compared with 13 in a generalized rodent, and the anticlinal spine is on the 12th rather than 10th thoracic vertebra, indicating a posterior shift of the back musculature. The greatly elongated tail is accomplished by lengthening individual vertebrae rather than adding additional segments and serves as a counterbalance in the absence of a long and flexible neck (Howell 1932).

As the jerboa is one of only a handful of obligate bipedal mammals and as there are closely related rodents that have retained quadrupedal locomotion, there is a wealth of opportunity to address the kinematics of bipedal locomotion and the mechanical interaction of this animal with its environment. As the shift to saltatorial bipedality reduces the function of the limb to a single plane, the only necessary muscles are those required for flexion and extension of the feet. Consistent with this, the jerboa has lost most of the intrinsic muscles of the feet required for adductive, abductive, and rotational movements (Howell 1932; Berman 1985). In collaboration with Dr. Andrew Biewener at Harvard University, we are investigating the gait patterns and impact forces of the jerboa over a range of locomotor speeds. In addition to multiple gaits within a species, there appear to be differences between species such that some individuals proceed at low speeds by a symmetrical “crow hop,” whereas others walk asymmetrically. Additionally, within the three-toed jerboas, the plantar surface of the digits is covered with long tufts of bristly hair that in radiographic analysis appear to support the full weight of the animal as it walks across a substrate such that only the nails and not the digits themselves come into contact with the ground. It is possible that this wiry tuft of hair acts somewhat like a snowshoe on the soft shifting sand dunes in their native environment.

GENETICS, GENOMICS, AND ASSOCIATED RESOURCES

The loss of lateral toes in the three-toed jerboas arose at least 8 million years after their divergence from the common ancestor of the five-toed jerboas, and the elongation and fusion of the metatarsals first occurred >20 million years ago. As a consequence, there are no closely related animals with different limb morphologies that could be anticipated to cross-breed and be interfertile, making the jerboa unamenable to a classical genetic and quantitative trait analysis. Therefore, mechanistic investigations of evolutionary processes must be pursued using genomic tools and knock-in and knock-out strategies used in the laboratory mouse. Due to the relatively close relationship with the mouse and the frequent morphological and molecular comparison between species, we will use the established mouse nomenclature for jerboa genes and proteins.

Karyotype analysis determined that *J. jaculus* has a diploid number of 48 chromosomes (Ben Faleh et al. 2010), and the estimated genome size is ~3 Gb. Most of the autosomes are meta- or submetacentric with the exception of the small pairs, 22 and 23, that are acrocentric. Additionally, the sex chromosomes, X and Y, are submetacentric and acrocentric, respectively. As part of the Genome 10K initiative to sequence >10,000 vertebrate genomes (Genome 10K Community of Scientists

2009), the Broad Institute (Cambridge, MA) has begun to sequence the genome of *J. jaculus* obtained from the Harvard University breeding colony. The genome will be sequenced to 10-fold coverage using the Illumina HiSeq 2000 and will be assembled and annotated by early 2012. Additionally, the Broad Institute has plans to sequence a species of the genus *Allactaga*, the five-toed jerboas, and of *Sicista*, the birch mouse, which will provide genomic information from closely related species with intermediate and ancestral morphologies. In parallel with this effort, a 10-fold coverage genomic BAC library is being generated by the laboratory of Dr. Pieter de Jong at Children's Oakland Research Institute (Oakland, CA).

TECHNICAL APPROACHES

Jerboa embryos are of comparable size (~15% larger) and physical consistency to mouse embryos and develop with a concerted timing of various structures so that their staging follows closely with that of the mouse. As such, protocols that have been developed for the mouse (Hargrave et al. 2005; McLeod 1980) have consistently worked in the jerboa with the addition of a slightly increased time for permeabilization steps in whole-mount preparations to account for the difference in size. Additionally, although in situ hybridizations of nonspecies-specific probes have been reported to work for other animals (Abzhanov et al. 2004; Hockman et al. 2008), mouse probes tested in the jerboa give a high level of background almost fully obscuring the signal. For this reason, we now exclusively use jerboa-specific probe sequences. To date, partial cDNAs of 23 genes have been cloned from the jerboa for expression analysis.

Certain unique characteristics of the jerboa make its breeding and rearing in captivity a challenge that has required the development of novel housing conditions for success. These conditions are outlined in an accompanying protocol (see **Husbandry and Breeding of the Lesser Egyptian Jerboa, *Jaculus jaculus*** [Jordan et al. 2011]) with the goal of assisting others in the rearing of jerboas and to provide information that may be valuable in the housing and breeding of other exotic rodents.

ACKNOWLEDGMENTS

I would like to thank Dr. Cliff Tabin and Dr. Farish Jenkins for enthusiastic support and mentorship. Dr. Shaoyuan Wu and Dr. Fuchun Zhang provided assistance with field collections in China.

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Cold Spring Harbor Protocols

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Cold Spring Harb Protoc; doi: 10.1101/pdb.emo066704

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