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Developmental genetics in emerging rodent models: case studies and perspectives

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For decades, mammalian developmental genetic studies have focused almost entirely on two laboratory models: *Mus* and *Rattus*, species that breed readily in the laboratory and for which a wealth of molecular and genetic resources exist. These species alone, however, do not capture the remarkable diversity of morphological, behavioural and physiological traits seen across rodents, a group that represents >40% of all mammal species. Due to new advances in molecular tools and genomic technologies, studying the developmental events underlying natural variation in a wide range of species for a wide range of traits has become increasingly feasible. Here we review several recent studies and discuss how they not only provided technical resources for newly emerging rodent models in developmental genetics but also are instrumental in further encouraging scientists, from a wide range of research fields, to capitalize on the great diversity in development that has evolved among rodents.

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Introduction

Understanding how morphological traits form and evolve is a fundamental challenge in biology. Because of their small body size, short generation time, and high fecundity in captivity, rodents traditionally have served as major laboratory models to study mammalian genetics and development, in addition to a variety of other research fields, including, behaviour, physiology, and biomedical studies relevant in human disease. Two murine species have been the primary workhorses: the house mouse (*Mus musculus*) and the laboratory rat (*Rattus norvegicus*). Their key role in uncovering fundamental principles in developmental genetics has been predicated on the wealth of molecular and genomic resources that have been generated for these species — the genomes of *Mus* and *Rattus* were among the first mammalian genomes sequenced and annotated [1,2]; numerous laboratory strains have been produced and are maintained; and molecular and cellular tools for tissue staining, imaging and functional testing abound.

The availability of such resources has made rodent models, particularly *Mus*, a prominent system in which to infer the molecular basis of trait formation and evolution in other species for which direct experimentation is difficult. For example, functional studies relying on transgenic mice have allowed researchers to test hypotheses related to diverse morphological traits, including limb formation in bats [3], limb loss and penis formation in snakes [4••], sensory vibrissae and penile spine loss in humans [5], human hair pigmentation [6••], as well as hair thickness and eccrine sweat glands in specific human populations [7]. On the other hand, computational and molecular approaches have been used in laboratory mice to construct predictive developmental models. For example, experimental data from *in vitro* reconstruction of tooth formation in *Mus* allowed for the prediction of dentition patterns among rodents with various diets [8]. More recently, it was shown that modulation of signalling factors can recreate the dental transformations that occurred during rodent evolution [9••]. These studies, however, are limited to traits present in laboratory rodents, and identifying causal genetic variants and developmental processes is often difficult due to the evolutionary distance between the species compared and the extent of character variation.

Despite the unquestionable importance of *Mus* and *Rattus* in biological research, both species are members of a single family {Muridae} and thus, their morphologies, behaviours and physiologies represent only a subset of the range of phenotypic diversity that has evolved among rodents. Here we highlight why rodents, a large group of species displaying a remarkable diversity of traits, should no longer be viewed only as a 'passive' tool for understanding biological processes occurring in other species. Instead rodents can be used both as a prominent study system in which to investigate the origin and evolution of natural variation in a range of phenotypes (evolutionary biology) as well as testable systems to explore the molecular bases of

tissue and organ development (developmental biology). Due to recent advances in genomic and molecular techniques, we can now turn to the use of new rodent models that display ecologically and developmentally relevant traits to explore the molecular basis of character formation and evolution in unprecedented detail.

Trait diversity in rodents

Rodents represent the most taxonomically diverse order of mammals, comprising more than 2000 extant species that diverged between the Pleistocene and the middle Miocene, and radiated into multiple environments (reviewed in: [10]). Present on all continents but Antarctica, rodents have invaded all terrestrial habitats, adapting to desert heat (e.g., jerboas, kangaroo rats), extreme cold (e.g. lemmings, siberian hamsters), altitude (e.g., deer mice, guinea pigs), semi-aquatic life (e.g., beavers, nutria), and fossorial life (e.g., gophers, mole rats), among others. Because they occupy such a range of habitats, rodents have evolved a diversity of specialized morphologies. Skeletal architecture, for example, is a highly variable trait–individuals, populations and species have evolved differences in digit number, limb length, tail length, head and snout shape, and/or vertebrae number (reviewed in: [11,12]). Coat colouration, often offering background-matching camouflage in rodents, ranges from completely white to melanic, and may be homogeneous or distributed in a bicolored (i.e., light ventrum and dark dorsum) or more complex, periodic pattern (e.g., longitudinal stripes and dotted lines of chipmunks and pacas). Fur can be sparse (e.g., naked mole rats) or extremely dense (e.g., chinchillas), and hair can thicken to form spines (e.g., spiny mice, porcupines). Variation in behaviour has also evolved among species: rodents may be diurnal or nocturnal, solitary or gregarious, monogamous or promiscuous, herbivorous or insectivorous or even carnivorous. Finally, although less documented, physiological diversity exists: for example, the kidneys of desert-dwelling rodents concentrate urine [13]; wood rats and other mice have evolved resistance to toxic compounds found in plants [14]; and hibernating rodents, like thirteen-lined ground squirrels, have evolved thermogenic proteins that are activated during hibernation to support nervous tissue function at low temperatures [15]. Natural populations of rodents thus constitute a wide source of variation that is an opportunity to study directly, beyond the limits of comparative approaches with traditional laboratory models, the developmental pathways and cellular events (morphogenesis) governing the formation of mammalian traits and the mechanisms shaping their evolution.

Beyond *Mus* and *Rattus*: developmental genetics in emerging rodent models

While largely unexploited due to the technical challenges associated with studying novel species, studying the mechanisms underlying the remarkable diversity highlighted above is now a real possibility. First, a wealth of natural history is documented on the majority of species representing the major rodent groups, and phylogenetic relationships of the main evolutionary lineages have been well resolved [10,16,17]. Second, a growing number of species already have established breeding colonies: wild-caught house mice, deer mice, grasshopper mice, jumping mice, jerboas, gerbils, voles, thirteen-lined ground squirrels, hamsters (e.g. Chinese, Syrian, dwarf), guinea pigs, mole rats and chinchillas, to name a few. The feasibility of breeding additional new rodent species in modern laboratories has been demonstrated by the fact that some of these colonies are maintained (after a decontamination process) in pathogen-free animal facilities. Third, with the large number of soon-to-be available rodent genomes (e.g., Genome 10k Project; Broad Institute of MIT and Harvard Project; [18]) and the advent of techniques amenable to virtually any species [19,20], such as innovations in high throughput DNA and RNA sequencing analytical technologies (e.g., double digest restriction associated DNA sequencing [21], *de novo* transcriptome assembly), new molecular tools (e.g., retroviral and lentiviral constructs, gene editing through the use of CRISPR/Cas9), and imaging techniques–scientists from various disciplines are starting to integrate fields to take advantage of the endless phenotypic variation of wild animals. Here we review work from three groups that have done so in emerging rodent models displaying variation in limb structure, coat colouration and skin regeneration (see Figure 1).

Jerboas and limb modifications

Because limb formation is arguably one of the primary models for developmental patterning and tissue differentiation, bipedal rodents have attracted much interest. Several desert rodents commonly display modifications in the number of digits or length of the limb, likely as an adaptation for long-distance bipedal locomotion, often observed in species that occupy open habitats and cover great distances to find food and shelter. Cooper and colleagues [22] compared chondrogenesis of hind limb bones in lesser Egyptian jerboas (*Jaculus jaculus*; see Figure 1), which have fused and drastically elongated metatarsals in the hind limb, compared with laboratory mice. They showed that chondrocytes undergo several phases of growth during embryonic development, providing insights into the mechanisms of skeletal size regulation. This study established the utility of jerboas as a new rodent system in which to study the processes governing limb evolution. A second study focused on the three-toed jerboa (*Dipus sagitta*), a species in which the anterior-most and posterior-most digits and associated metatarsals are absent. Using histological and expression analyses for marker genes known for their role in digit formation in mice (i.e., *Shh*, *Gli1*, *HoxD13*, and *Ptch1*), they showed that during early development the three-toed jerboa undergoes patterning of five digits, similar to what is seen in