# Mobility as an Emergent Property of Biological Organization: Insights from Experimental Evolution

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Anthropologists accept that mobility is a critical dimension of human culture, one that links economy, technology, and social relations. Less often acknowledged is that mobility depends on complex and dynamic interactions between multiple levels of our biological organization, including anatomy, physiology, neurobiology, and genetics. Here, we describe a novel experimental approach to examining the biological foundations of mobility, using mice from a long-term artificial selection experiment for high levels of voluntary exercise on wheels. In this experiment, mice from selectively bred lines have evolved to run roughly three times as far per day as those from nonselected control lines. We consider three insights gleaned from this experiment as foundational principles for the study of mobility from the perspective of biological evolution. First, an evolutionary change in mobility will necessarily be associated with alterations in biological traits both directly and indirectly connected to mobility. Second, changing mobility will result in trade-offs and constraints among some of the affected traits. Third, multiple solutions exist to altering mobility, so that various combinations of adjustments to traits linked with mobility can achieve the same overall behavioral outcome. We suggest that anthropological knowledge of variation in human mobility might be improved by greater research attention to its biological dimensions.

Anthropologists use the term "mobility" to refer generally to how humans move around their landscapes. Here, we define mobility more narrowly as the total distance of daily travel. Anthropological interest in mobility is understandable. As Robert Kelly[1] once noted, few images in anthropology are more iconic than that of a small group of hunter-gatherers trekking through the wilderness, and such images have reinforced a popular narrative about how life in post-industrial societies differs from that of our ancestors: We are generally sedentary, while hunter-gatherers travel a lot and are generally more physically active. With our shift toward a sedentary way of life have come numerous accompanying changes, including how we exploit environmental resources, the abundance of technology in our lives, and the modes and intimacy of our relationships with each other. These attendant changes in economy, technology, and social relations highlight the fact that mobility is not a discrete phenomenon, but rather a nexus that connects many critical aspects of human cultural life.

As importantly, mobility is also inextricability linked to human biology in that it emerges, as all of our behaviors do, from multiple integrative levels of our biological organization, including anatomy, physiology, neurobiology, and genetics. However, anthropologists have done surprisingly little exploration of the biological foundations of mobility relative to research on mobility's relationship to culture. In this short review, we aim to call greater attention to the concept of mobility as an emergent property of biological organization and to identify a few potential domains of anthropological research. To this end, we describe a novel experimental model involving laboratory house mice that illustrates well how mobility arises from complex and dynamic interactions among numerous biological traits. We focus on three key insights gleaned from this experiment that can be considered foundational principles in the evolutionary study of mobility, and which may be useful for generating anthropological hypotheses.

## HIGH RUNNER MICE

Wild animals exhibit tremendous variation in mobility. Wolves, for example, occupy large home ranges and travel long distances on a daily basis. In contrast, deer living in the same area move around much less. On the face of it, one might suspect that this is simply because wolves must

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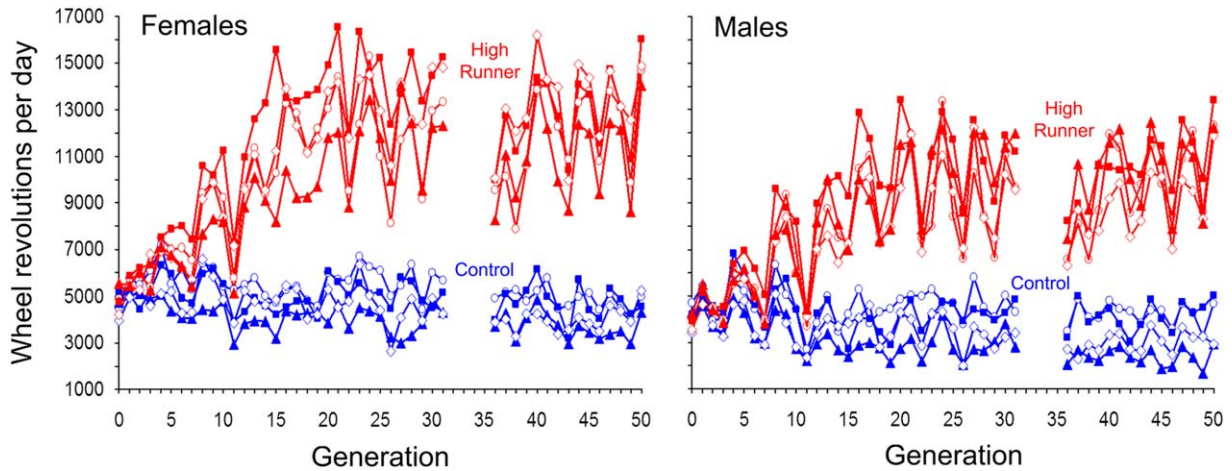
Figure 1. Voluntary wheel-running distance (mean daily revolutions; wheel circumference = 1.12 meters) for each of the eight lines on days five and six of a six-day exposure to wheels. The drops in wheel running that occur approximately every four generations (especially in males) among both High Runner and control lines correspond to generations tested during the summer. It is not yet known whether this represents an endogenous annual cycle or possible changes in humidity (and sometimes temperature).[4,6] For both High Runner and control lines, roughly one-third of daily wheel revolutions are attributable to "coasting."[15] After generation 31 of the experiment, mice were moved from the University of Wisconsin-Madison to the University of California-Riverside, and wheel running was not measured (nor was selection applied) for four generations. (Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.)

move more to get the prey resources they need, whereas deer, who eat plants that are easy to find, do not need to move as far. But might there be something more to it than this? Perhaps some of the variation in mobility among species, or among populations within species, is related to differences in the brain or body that either compel certain individuals to move greater distances or allow them to move greater distances. That is, variation in mobility may be determined by biological characteristics that are, at least in part, genetically based and, to some extent, inherited from parents within species and from other species in a phylogenetic, macroevolutionary sense.[2]

To address this general hypothesis at the level of microevolutionary changes within a single species, Garland and colleagues[3–6] have been conducting an experiment in which mice are selectively bred for voluntarily high running distances on wheels, which are a convenient way to record one aspect of mobility. This strategy was based on the reasoning that if mobility levels have no genetic basis, then selective breeding for high mobility could not possibly result in change over time. On the other hand, if mobility has some genetic basis, then it should evolve in the direction that selection favors.

The selection experiment[3–6] began in 1993 with a base population of 224 genetically diverse (outbred) mice, from which eight closed lines were established: Four of the eight lines were designated as selected High Runner lines; the other four lines were kept as nonselected controls. In each successive generation, when mice were between six and ~eight weeks of age, they were individually housed with access to running wheels (1.12-meter circumference) for six days. Daily wheel revolutions were recorded by a computer-automated system. The selective breeding criterion was the total number of wheel revolutions on days five and six of the six-day test. Days 1–4 were ignored to avoid selecting on neophobia or neophilia. In the four High Runner lines, the highest-running male and female from each family were chosen as breeders; in the four control lines, a male and female from each family were randomly chosen. No sibling mating was allowed in any line.

All of the High Runner lines responded to selection and, between generations 17 and 27 of the experiment, reached limits depending on line and sex. At the selection limits, mice from the High Runner lines ran roughly three-fold more than did those from the control lines (Fig. 1).[6] This difference has persisted for more

than 40 additional generations of selective breeding.[7] Selected mice regularly run more than 15 kilometers per day, which is a phenomenal distance for animals weighing less than 50 grams. Importantly, although the selection regimen specifically focused on wheel-running behavior, it also led to a significant increase in how active High Runner mice are in their home cages when not given wheel access.[8,9] Therefore, it truly is a general high-mobility phenotype displayed by selected-line animals, which lasts for most of the life span.[10,11]

The fact that running behavior was increased by artificial selection demonstrates that mobility is influenced by genetic factors. The magnitude of this influence in the starting population can be referred to as the narrow-sense heritability of mobility, defined as the proportion of variance in mobility attributable to additive genetic variance. Narrow-sense heritability for wheel running among the High Runner mice has been estimated in various ways (for example, offspring-on-parent regression and response to selection over the first several generations), all of which have yielded values of around 0.25.[3,6] Interestingly, this value is very close to the average heritability estimate for physical activity level among humans derived from family resemblance studies,[12]

although reported heritability estimates of human physical activity range rather widely (between 18% and 92%),[13] likely reflecting the greater difficulty of controlling for environmental variables in humans than in experimental animals.

Once it was determined that wheel-running behavior has a heritable component, the primary goal of the selection experiment became to better understand how mobility evolves with respect to aspects of performance, structure, and function in terms of both motivation and ability.[4] For the past 20 years, researchers from around the world have contributed to accomplishing this goal. Their efforts have resulted in well over 120 peer-reviewed journal articles, all of which can be freely downloaded at: http://www.biology.ucr.edu/people/faculty/Garland.html. Although each study involving High Runner mice is motivated by specific researcher interests and questions, together they form a synergistic and complementary body of work. Of the many evolutionary insights gleaned from this research program, three stand out that specifically pertain to the integrative levels of biological organization that give rise to mobility.

## THREE INSIGHTS

1. *Evolutionary changes in mobility will be associated with alterations to many biological traits.*

As an emergent property of biological organization, mobility patterns arise from numerous interacting secondary traits (Fig. 2).[4,7,14] As a consequence of this dependence of mobility on lower-level (subordinate) biological traits and their interrelationships, an evolutionary response to selection among High Runner mice has generated a cascade of concomitant changes in aspects of organismal performance, as well as suborganismal features of anatomy, physiology, and biochemical pathways affecting both behavior and performance capacity.

At the level of organismal performance, a primary difference between High Runner mice and nonselected mice is their voluntary running speeds on wheels. Although an evolutionary increase in daily running distance among selected mice could be achieved by increasing running speed, time spent
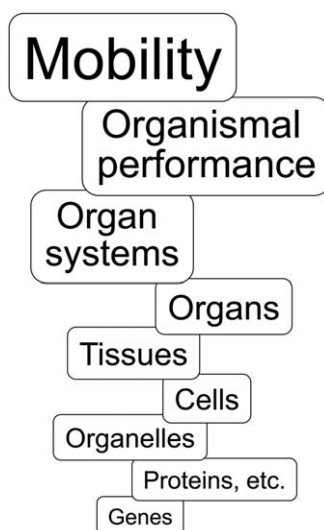


Figure 2. Mobility emerges from multiple integrative levels of biological organization, including organismal performance and a wide variety of suborganismal anatomical, physiological, and biochemical traits. Modified from Garland and Kelly.[14]

running, or both, daily running duration has changed much less across generations than has running speed,[3,15–17] which has increased more than two-fold.[17] In addition, selection has led to increases in maximum aerobic capacity (VO$_2$max) and endurance, respectively measured as the maximum rate of oxygen consumption and the distance or duration run to exhaustion during forced treadmill exercise.[18–20] This is consistent with evidence from a phylogenetically diverse sample of mammals that VO$_2$max exhibits a weak positive correlation with home range area.[2]

Locomotor economy has also improved in High Runner mice in that, because of their small size, they have low whole-body locomotor costs, quantified as the amount of oxygen consumption required per unit of running distance.[21] Increased running distance in High Runner mice has been coupled with an increase in the intermittency of locomotion,[16] which may contribute to reducing locomotor costs and/or increasing endurance capacity.

At the suborganismal level of organ structure and function, a particularly interesting and recent finding is that High Runner mice have larger brains than nonselected mice do.[22] This result parallels a cross-species comparison in mammals that showed a positive association between mass-corrected brain

size and VO$_2$max.[23] Perhaps surprisingly, the cerebellum of High Runner mice is not enlarged, but MRI analyses of *ex vivo* brains indicate relatively larger midbrains than those in nonselected mice.[22] The midbrain is known to be essential for such functions as reward learning, motivation, and reinforcing behavior. Thus, the derived larger midbrain size of High Runner mice may contribute to a heightened reward system and motivation to run. Moreover, the midbrain is involved in controlling movement, so size enhancement may affect not only propensity to run, but also ability.[22]

Other notable examples of correlated responses to selection have been identified in the musculoskeletal system.[5] For example, the limb bones of selected mice have larger joint surfaces[24–26] and thicker shafts than those of nonselected mice,[25–27] which likely lowers joint stresses during running and makes the bones more resistant to fracture. Importantly, these bony features are present shortly after birth — before the onset of locomotion — indicating that they are not solely the result of lifetime physical activity *per se*, but rather their derived genetic architecture.[28] High Runner mice also have skulls with distinctively shaped semicircular canals,[29] which sense head movement and aid in the coordination of locomotion. Such changes in brain size, limb bone robusticity, and inner ear morphology are especially interesting from an anthropological perspective, since similar changes also appear in the hominin fossil record with the advent of endurance-running capabilities in the genus *Homo*.[30–32] The increased symmetry of hind limb bone lengths in High Runner mice has a parallel in the world of thoroughbred horse racing.[24]

At the level of biochemistry, the most influential changes established to date are perhaps those that have occurred in neurobiological signaling pathways that affect motivation.[33,34] The neurobiological profile of High Runner mice bears a striking resemblance to human attention deficit hyperactivity disorder (ADHD) and is also consonant with heightened motivation for exercise as a natural reward (such as "runner's high").[33] For example, both ADHD and motivation for natural rewards have been related to changes in the chemical

activity of the neurotransmitter dopamine, and High Runner mice react differently than nonselected mice do to the administration of dopamine drugs.[35,36] In particular, drugs that block the normal function of dopamine transporter proteins, such as Ritalin and cocaine, significantly reduce running levels in High Runner mice, but do not do so in mice from the nonselected control lines.[35,36] Furthermore, dopamine release is facilitated by the endocannabinoid system, which activates cannabinoid receptors in brain reward regions during and following exercise. High Runner mice exhibit distinct responses to pharmacological treatment with cannabinoid CB1 receptor agonists and antagonists.[37,38] Specifically, the administration of such drugs decreases wheel running in both selected and control mice, with some sex specificity, but to a far greater extent in High Runner mice.[37,38] Again, this is interesting from an anthropological perspective, since recent experimental evidence from humans suggests that an evolutionarily derived form of endocannabinoid signaling may also explain, at least in part, why humans frequently and willingly engage in endurance-running exercise.[39]

Besides these correlated responses to selection, numerous others have been documented at all levels of biological organization.[4–7,33] Although many can be interpreted as adaptive in that they may improve motivation or ability to run, it must be emphasized that some observed correlated responses have no obvious direct link to running propensity or capacity. For example, it has been observed that High Runner mice build smaller nests in their home cages,[40] display greater predatory aggression toward crickets,[41] and have a slightly altered finger digit ratio.[42] Such seemingly arbitrary changes probably arise as the result of the phenomenon known as pleiotropy, in which one gene simultaneously contributes to multiple phenotypic traits, some of which augment performance and others that do not. (Pleiotropy may occur for many reasons, including shared developmental pathways or hormonal influences.) The important point to keep in mind, however, is that all of the associated changes detected in the selection experiment, whether directly or indirectly related to wheel running, illustrate the fact that because mobility emerges from a variety of dimensions of biological organization, it cannot evolve without changes in a suite of other traits.

2. *Evolutionary changes in mobility will result in trade-offs and constraints among associated traits.*

Because mobility depends on so many traits at various lower levels of biological organization, its independent evolution will inevitably be constrained by the degree to which correlated responses to selection negatively affect other aspects of performance that influence one or more components of individual Darwinian fitness (survival and reproduction). For example, if selection for high mobility were to result in correlated deterioration in gonadal function, then little evolutionary change in mobility would be possible without impairing individual reproductive success. When traits that influence one type of performance cannot be improved by selection without worsening traits influencing another type of performance, there is an evolutionary trade-off.[43] This idea of trade-offs is a critical conceptual tool for understanding how traits have evolved in a correlated fashion among High Runner mice.

A prime example of an evolutionary trade-off relates to a subset of mice from the selection experiment that has become known as the "mini-muscle" mice. Early in the experiment, it was recognized that some mice in three of the eight lines (two selected, one control) displayed a phenotype characterized by a 50% reduction in the mass of the calf muscle complex,[44,45] which plays a major role in propulsion during mouse locomotion. Comparisons between offspring and parents indicated that the phenotype was inherited through a single recessive genetic variant (the so-called "mini-muscle allele").[44] Recent research has identified the precise polymorphic gene.[46] In the one control line that had mini-muscle individuals, the phenotype was expressed only rarely; eventually, it was entirely lost as a result of random genetic drift.[5,44] In contrast, in the two High Runner lines that showed the phenotype, the frequency of the mini-muscle phenotype increased dramatically and rapidly across generations, indicating that the allele has been favored by the selection regimen.[44] Importantly, mini-muscle individuals appear no different from wild-type mice in terms of gross external morphology or behavior. The selection that favored the mini-muscle phenotype was entirely unintentional.

Why has selection promoted the mini-muscle allele? One possible reason is that for animals that devote much of their total energy budget to locomotion, lightweight muscles are advantageous because they may reduce the energetic cost of cycling the limbs.[25,27,44] Furthermore, individuals exhibiting the mini-muscle phenotype have been shown to have muscles with greater aerobic capacity on a per-unit mass basis,[45] primarily as a result of a distinct composition of muscle fiber types. Specifically, mini-muscles are made up of many slow-twitch fibers and few fast-twitch fibers.[47,48] Slow-twitch fibers are more efficient at using oxygen to generate fuel for continuous muscle contractions over a long time.[49] In this way, the mini-muscle phenotype resembles that of many elite human endurance runners.[50] It is also worth noting that the two High Runner lines without mini-muscles have also evolved slightly smaller triceps surae muscles;[44] hence, overall, High Runner mice resemble human marathoners in having reduced muscle mass.

However, there is a trade-off: Although mini-muscles might be advantageous for running long distances, they are not good for sprinting. Muscles beneficial for sprinting are those that are large and composed mainly of fast-twitch fibers to enhance power output for short, fast bursts of anaerobic activity; in other words, the exact opposite of the mini-muscle phenotype. Therefore, not surprisingly, in a study of running speed on a race track in mice from three of the four High Runner lines, one in which the mini-muscle allele has become fixed and two in which the phenotype has never been observed, the maximum sprint speed of the mini-muscle mice was, on average, 13% and 31% lower than that of mice from the other two selected lines.[51] This is a classic example of a trade-off between stamina and speed that is often, but not always,[52] seen among

animal species (for example, between dogs and cats) and among professional athletes (for example, the best marathon runners are not the best sprinters).[43]

Other notable examples of evolutionary trade-offs among High Runner mice are evident at the level of endocrine physiology. For example, relative to controls, mice in the four selected lines have roughly two-fold higher levels of circulating corticosterone,[8,53,54] a steroid hormone produced in the adrenal glands. In terms of wheel-running performance, this may be beneficial for High Runner mice because corticosterone is known to be important in mobilizing energy reserves during sustained locomotion.[8,54] Specifically, corticosterone promotes the production of glucose and free fatty acids, which provide the energy required for persistent muscle contraction. Moreover, given that cortisone has been shown to increase the neurological reward value of certain behaviors, such as administration of drugs and ingestion of sugars and fats, elevated corticosterone may improve motivation to run.[8] But even though elevated corticosterone concentrations may in some ways be advantageous for locomotor activity, they may also have deleterious effects on High Runner mice, including not only the suppression of growth[53] and possibly immune function,[55] but the fostering of certain depression-like behaviors.[9] Therefore, like many traits, higher corticosterone levels appear to involve both benefits and costs.

These and other examples from the selection experiment highlight the point that when emergent traits like mobility form a nexus with numerous other dimensions of biological organization, it is unlikely that all of the associated changes will be positive for all types of organismal performance. Ultimately, the exact phenotypic outcome of selection acting on mobility will represent a compromise of sorts among the many traits tied to mobility, as well as other traits targeted by selection.

3. *Multiple solutions exist to altering mobility.*

In selective breeding experiments, a key advantage to having multiple populations under selection is that it permits researchers to discover multiple solutions to the adaptive problem posed by the selection regimen.[4,7] The adaptive response to selection of a given population will inevitably depend on the genetic (allelic) variation within it, which will change across generations as a result of selection and such stochastic processes as mutations and genetic drift. Therefore, because particular alleles are available only in certain populations, different populations may evolve distinct but potentially equally adaptive phenotypes.[4] A nice example of this from the selection experiment is the mini-muscle allele. The two High

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Runner lines in which the mini-muscle allele was present were able to use it, whereas mice in the other two High Runner lines that lacked the allele had to make do without it.[4,6,44] Yet, on average, the two lines with and two without the allele do not differ in how much they have responded to selection.[6,17]

Another excellent example of multiple solutions is the variation present among the four High Runner lines and between the sexes in their wheel-running speeds and durations (Fig. 3).[17] As stated earlier, High Runner lines complete, on average, roughly three times more wheel revolutions per day than do the nonselected lines,[4–7] primarily because of their higher running speeds.[3,15–17] Importantly, all selected lines have displayed a similar fold increase in daily revolutions, so that, in later generations, running distances among them do not differ significantly.[17] However, High Runner lines do exhibit significantly different running speeds and durations, with the consequence that individual lines have achieved the three-fold increase through distinct adjustments in average running velocity and time spent running.[17] Therefore, the selection regimen has evidently been conducive to phenotypic divergence at the level of biological organization immediately below that of the trait under selection.[17] In addition, the response to selection has differed to some extent between females and males. Both sexes have evolved the three-fold increase in running distance, but in males this has involved a somewhat greater increase in running duration than in females.[3,15–17]

The essential point to bear in mind about multiple solutions to selection is that because emergent traits like mobility are shaped by so many aspects of biological organization, there is potential for a variety of combinations of adjustments to traits networked with mobility to achieve the same overall behavioral outcome.

## MOVING FORWARD

Each of the papers in this issue of Evolutionary Anthropology in some way addresses a single question: What is missing in the anthropological study of mobility? We respond to this by encouraging anthropologists to consider directing greater attention toward mobility's biological foundations. The anthropological literature on mobility is vast, but the bulk of it pertains specifically to mobility's relation to cultural variation, especially those aspects of culture that register in the archeological record.[1] With few exceptions,[31,32,39] the effects of our biology on mobility have been largely overlooked. Thus, there is great potential for increasing anthropological knowledge of mobility by expanding the scope of inquiry to include both biological and cultural agents. Human mobility is, after all, a truly biocultural phenomenon.
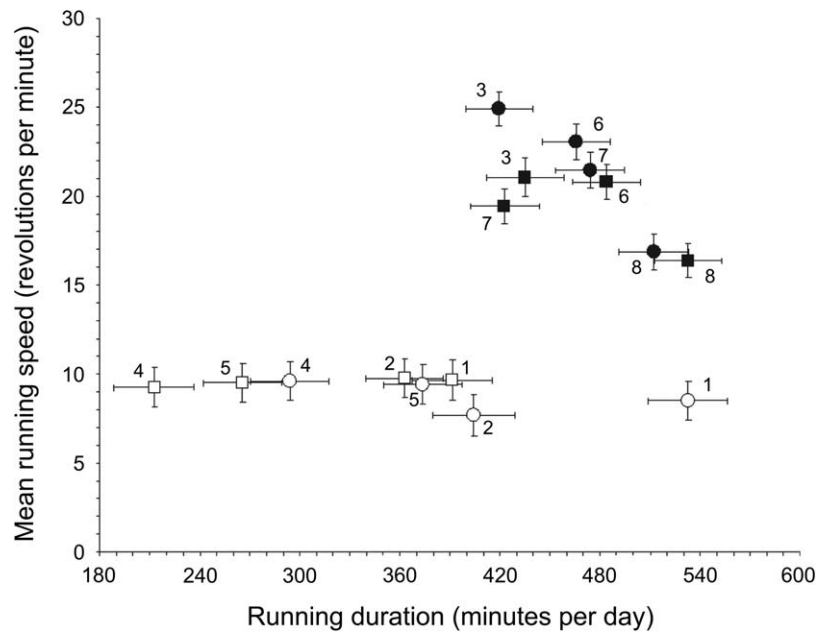
Figure 3. Voluntary wheel-running speed and daily running duration for each of the eight lines at generation 43 (least-squares means ± standard errors).[17] Filled circle, High Runner female; filled square, High Runner male; open circle, control female; open square, control male. Laboratory designated line numbers are provided. Based on the partial correlation between speed and duration of running, controlling for sex, the High Runner lines show a significant negative relation ("trade-off"), but the control lines do not. Modified from Garland and colleagues.[17]

Future anthropological research on mobility's biological foundations might proceed along at least two paths, through studies of variation among living human populations and analyses of evolutionary change in other species, both at micro- and macroevolutionary scales.[2,23] As underscored by the High Runner mice, variation in mobility emerges from complex and dynamic interactions between numerous biological traits that both compel and enable certain populations to be more mobile than others. We suspect that variation in mobility among human groups also stems, to some extent, from such biological differences, perhaps in both the brain and body, affecting both motivation and performance. Many anthropologists may be skeptical of this idea, but it leads to a multitude of testable hypotheses concerning biological differences among human populations. At the scale of microevolution, the High Runner mice illustrate that when selection acts on mobility, associated changes in biological traits are numerous and complicated, but nevertheless consonant with well-established biological principles. The three principles emphasized here—

correlated evolution, trade-offs, and multiple solutions—almost certainly apply also to the alterations in human biology that gave rise to evolutionary changes in mobility, irrespective of the many cultural effects. Thus, we hope that, moving forward, research on the High Runner mice might be of value in generating anthropological hypotheses about the biological foundations of human mobility. At the same time, future work on the biology of human mobility may motivate and inform additional studies of other species.

With respect to the High Runner mice as a model for human mobility, it would be interesting to examine their group behavior in larger, semi-natural enclosures and see if that behavior in some ways parallels the behavior of highly mobile human groups (for example, by being less hierarchical and more cooperative, as are many hunter-gatherer populations). It would also be interesting to examine trade-offs that may occur when these mice need to reproduce when they have access to wheels or perhaps are required to run to obtain food, conditions that are similar to those of mobile human populations in which pregnant women must continue to forage and do other kinds

of physical work. All models are abstractions of the phenomena they purport to depict. We certainly recognize the many limitations of the High Runner mice, but we also assert that the several parallels between their evolutionary trajectories and those observed in "mobile" wild species confers on them some degree of face validity.

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