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## EVOLUTION

# On the origin of Peter Rabbit

Domestication of rabbits led to changes across the genome, particularly in regions related to brain development

By Kirk E. Lohmueller

Which genetic changes occur when animals are domesticated, or selectively bred in order to increase the frequency of characteristics that humans find desirable? Studies aiming to address this question can not only reveal the biological basis of important phenotypes, but also provide a glimpse into the mechanisms of rapid evolutionary change. On page 1074 of this issue, Carneiro *et al.* (1) report a population genomic study of rabbit domestication that shows that there is no single “domestication gene.” Rather, many genetic variants across the genome have been affected by natural selection throughout domestication. Further, these variants tend to be in regulatory regions located in genes related to brain development.

Advances in genomic technology have allowed researchers to compare the genomes of wild and domesticated populations in search of genetic changes associated with domestication. Recent studies on domesticated chickens (2), pigs (3), and dogs (4) have found candidate regions for selective sweeps—or areas of the genome where natural selection has increased a favorable allele to high frequency—associated with domestication. However, they did not assess the broader evolutionary questions regarding the type of genomic changes and mechanism of selection involved.

Rabbits provide a potentially powerful system to study the genetics of animal domestication. Historical records and previous genetic work (5) suggest that rabbits were domesticated from a single wild population in Southern France about 1400 years ago. The domestication process for rabbits thus appears to have been simpler than that for other species, which have either undergone multiple independent domestication events (6) or experienced extensive back-crossing with wild populations (7, 8). Further, non-domesticated descendants of the ancestral rabbit population are readily available, providing a control group that may not be available for other species.

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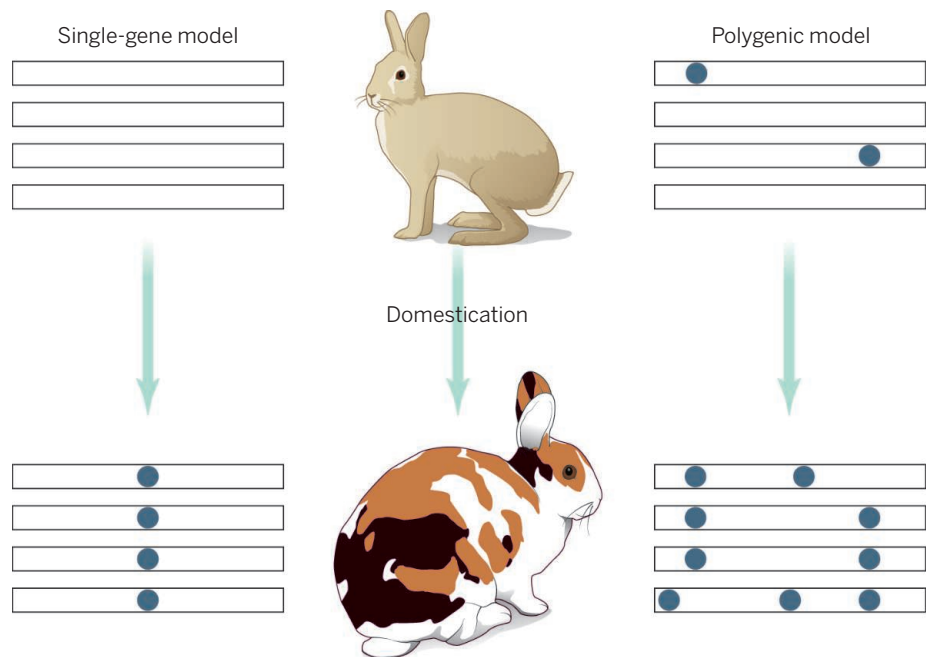
To search for the genetic changes associated with rabbit domestication, Carneiro *et al.* performed whole-genome sequencing of six breeds of domestic rabbits, wild rabbits in Southern France (descendants of the same putative ancestral population as the domesticated rabbits), and wild rabbits from the Iberian Peninsula. This sequencing strategy allows for relatively unbiased estimates of allele frequencies at variable sites across the genome.

The authors then searched for signatures of selection in domestic rabbits using two statistical methods. First, they looked for regions of the genome that have large differences in allele frequency between domestic and wild rabbits and that also show reduced genetic variation. Both patterns are signatures of selective sweeps (9). A major strength of the study is that the authors attempt to control for population history by assessing the probability of these patterns under models of population history that do not include selection. No individual region of the genome had patterns of variation so unexpected that they could not be

explained by population history alone. However, the authors found roughly twice as many unusual regions in the data as expected under models with only population history, suggesting that population history, without natural selection, cannot explain the genome-wide patterns of variation. Second, the authors used a model-based test for selection (10) and found 78 regions that were significantly unusual under their demographic model, even after accounting for the number of statistical tests performed. Taken together, these results provide strong evidence for selection at many loci throughout the genome.

Carneiro *et al.* then examined the types of functional changes that may underlie these sweeps. Those variants showing the largest differences in frequency between wild and domesticated rabbits tend to be located more often than expected by chance at conserved noncoding regions, untranslated regions, and coding regions. Variants showing less extreme differences in allele frequency between wild and domestic rabbits were still enriched in untranslated regions and conserved noncoding regions. However, the enrichment in coding regions disappeared. These results suggest that domestication involved shifts in allele frequency at many loci across the genome and that these variants may be regulatory, rather than coding.

Finally, Carneiro *et al.* examined how the variants showing the largest differences in allele frequency between wild and domestic



**Two models of the genetic basis of domestication.** In the single-gene model, a single mutation increases in frequency as a result of positive selection and is carried by all the domesticated animals. In the polygenic model, domestication occurs by changes at many genetic variants, each of which has an individually small effect. Carneiro *et al.* favor the polygenic model for rabbit domestication.

rabbits cluster into biologically functional categories. The categories showing the most significant enrichment of differentiated variants were related to nervous system development. Additionally, the differentiated variants preferentially occurred in genes that, when disrupted in mice, give rise to defects in the nervous system. These results suggest that selection during domestication may have affected genes relating to specific behaviors, perhaps those allowing the animals to better interact with humans.

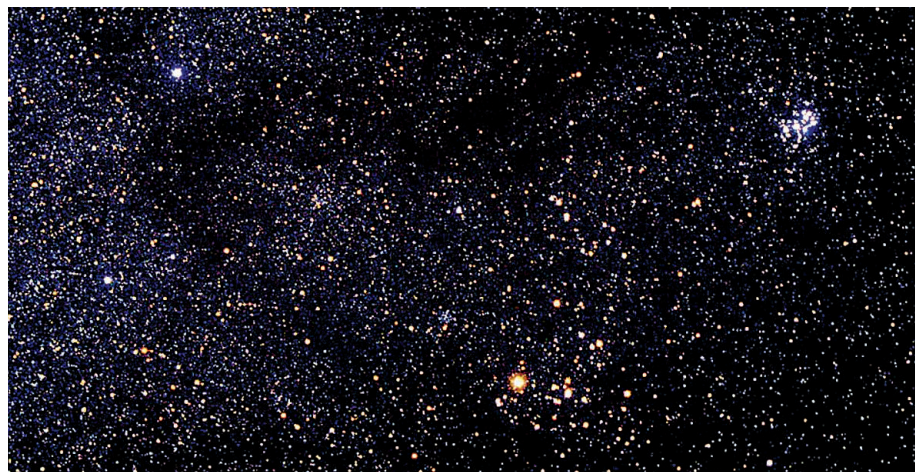
The study of Carneiro *et al.* adds to the growing literature suggesting the importance of polygenic adaptation as an evolutionary process (see the figure) (11, 12). In addition to there being many putatively selected variants, rabbits show other patterns often associated with the polygenic model. For example, at least some of the selection occurred on genetic variation that already existed in the population, rather than on new mutations. Second, many of the putatively selected variants are not carried by all of the domesticated rabbits. These findings do not rule out the occurrence of classic selective sweeps, in which the selected allele becomes fixed in the population. Indeed, Carneiro *et al.* also found evidence of such sweeps. Rather, the results suggest that both mechanisms are likely occurring.

It is tempting to compare the genomic properties of selection during domestication in rabbits to that in other species, such as dogs, pigs, horses, and chickens. However, such a comparison is fraught with complications at the present time. The genomic studies in the different taxa use very different designs and statistical methods. A proper comparison of the key attributes of selection during domestication awaits systematic genome resequencing across the multiple taxa, combined with application of the same statistical methods to the data. Such comparative population genomic analyses promise to reveal general insights into the domestication process and how rapid evolution under strong selection operates across genomes. ■

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**Taking a measure.** A view of the Taurus constellation, including two stellar clusters whose distances were provided by the Hipparcos satellite. The Pleiades (top right) and the Hyades (bottom center, slightly to the right of the bright red star Aldebaran). Only the Pleiades distance has been controversial, raising the possibility that hydrogen-burning stars in the Hyades and Pleiades could be intrinsically very different in their fundamental properties.

#### ASTRONOMY

## One good cosmic measure

Radio-wave interferometry provides an accurate measurement of cosmic distances

By **Léo Girardi**

As Earth orbits around the Sun, nearby stars are seen to move against the background of more distant stars and galaxies. The angular amplitude of this motion is called parallax and provides a direct, trigonometric measurement of the stellar distances as compared to the size of Earth's orbit. A great achievement of the European Space Agency's satellite Hipparcos (1) was the measurement of parallaxes of over 100,000 stars simultaneously, making it widely recognized as having provided accurate distances to thousands of normal stars and to a few star clusters. Since the first release of the Hipparcos results in 1997, however, it was noted that the distance obtained for the Pleiades star cluster was abnormal (see the figure). Its hydrogen-burning stars, when compared with stars of similar effective temperature in other well-measured clusters like the Hyades, appeared to be systematically too faint, were the Hipparcos-derived distances adopted. The effect implied either that the Hipparcos distances were too short or that Pleiades hydrogen-burning stars had some very peculiar property, such as an extremely high fraction of helium in their interiors (2). On page 1029 of this issue, Melis *et al.* (3) present new observations of stars in the Pleiades cluster, demonstrating that the Hipparcos-derived distances were indeed off

by 10%. Their radio-wave interferometry approach thus demonstrates a precise and accurate method to determine stellar distances.

For the Pleiades cluster, Melis *et al.* point decisively to a distance of 136 parsecs, which is essentially the same distance expected by the stellar physicists under the assumption that hydrogen-burning stars share the same intrinsic properties, independently of the clusters where they are born. Melis *et al.* applied a completely independent technique, using very large baseline interferometry at radio wavelengths to measure the angles between five Pleiades stars and a background quasar. Even if skepticism about the Hipparcos distance to the Pleiades has somewhat prevailed among the stellar-modeling community, now it should be more widely apparent that the problem is not in understanding what weird stellar physics could be going on in the Pleiades hydrogen-burning stars. The problem is understanding what went wrong with the Hipparcos measurements.

Hipparcos used a simple, if revolutionary, approach whereby the entire sky was continuously scanned over 3 years. Using two slits separated by 58°, there were multiple measurements for each star of its position with respect to those of widely separated stars; their best-fit positions, angular velocities, and parallaxes could be derived by performing a global optimization of the astrometric solution. However, a careful examination of