

Comment

## Foxes and hounds

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I hadn't planned to write another column about the dog genome, but they insisted. Not my editors - their helpful suggestions usually take the form of "You're writing about WHAT?". It was Mink and Clifford, the two dogs who generously allow me to share their house in return for food, regular walks, throwing of tennis balls, and a copious supply of doggie treats. Ever since my column on the 1.5x draft dog genome sequence (*Genome Biol* 2003, **4**:120), they have been trying to convince me that the most important part of the story had been overlooked by most of the pundits. Now that the new 7.5x sequence has been released (Lindblad-Toh *et al.*: *Nature* 2005, **438**:803-818), they've been pestering me constantly. So I decided to revisit the topic, not only to keep them happy (though I do a lot of things for that reason alone), but also because I must admit they have a point.

Much of the excitement over the original 1.5x dog genome sequence, which was from Celera and covered about 75% of the 2.4 billion base pairs that comprise the 39 chromosomes of *Canis familiaris* (albeit with gaps in many genes), concerned the implications that a better understanding of canine biology would have for human biology. The extraordinary phenotypic diversity of the more than 500 different breeds of dogs (of which about 150 may qualify as distinct subspecies since they are reported not to exchange genes) has arisen in less than 50,000 years (although the exact time of domestication of the Asian grey wolf, the ancestor of all modern dogs, is uncertain). And since each pure breed - for example, Mink is a chocolate Labrador Retriever - is an isolated genetic population, their distinct morphological (for example, brown fur, big nose, drools a lot) and behavioral (lazy, big-hearted, always hungry) phenotypes can in principle be linked to specific genetic changes. The new science of behavioral genomics should get an enormous boost from the new, essentially complete (99% coverage) dog genome sequence. So should evolutionary and developmental biology. And much has already been written about the implications for human health: like most inbred strains, pure dog breeds are susceptible to specific illnesses

(hereditary kidney cancer, for example, occurs only in German Shepherds, and epilepsy is found in certain other breeds), making the identification of disease genes relatively easy. Veterinarians have already found over 500 canine diseases that are similar to human hereditary diseases, and have used the dog to identify 25 associated genes. (Hybrid vigor is just one of many things that lead Clifford, a mixture of Cocker Spaniel and French Poodle, to believe that he is superior to his step-brother. Evidence suggests that, if this is true physically, it is certainly not true mentally.)

But that isn't what Mink and Clifford wanted me to write about. What fascinates them is that with the completion of the dog genome sequence the first step has been taken in understanding one of the most remarkable, and mysterious, phenomena in biology: domestication.

It would be hard to overemphasize the importance of domestication of wild animals in human progress. Jared Diamond devotes a huge section of his fascinating book, '*Guns, Germs and Steel*', to the role that domestic animals played in the development of civilization. Until the invention of the steam engine, for over 100,000 years no human could travel faster than a horse could carry him or her, or haul a load greater than an ox could pull. Domestic animals made farming possible, which in turn allowed previously nomadic people to become settled, which in turn led to the creation of cities and permitted the rise of a leisure class that could focus its attention on philosophy, the arts, and scientific research. Diamond argues persuasively that the mere presence of domestic animals, and the consequent exposure of their human companions to the milder forms of infectious diseases that they carried (cowpox versus smallpox, for example), gave cultures with such animals an enormous competitive advantage over cultures that lacked them.

The dog was the first animal to be domesticated, and its single ancestor, the wolf, is still available in essentially original form as a basis for detailed comparison. Since the first 1.5x draft dog

genome sequence was that of a poodle while the latest one comes from a boxer, we already have two different breeds to compare in some detail. About ten other breeds have had enough partial sequencing done (about 6%) to allow a large compendium of single-nucleotide polymorphisms (SNPs) to be derived. This information already gives some clues about the domestication process that led to *Canis familiaris*. Linkage disequilibrium within breeds extends over distances of several megabases, while across breeds the distance is typically tens of kilobases. Lindblad-Toh *et al.* interpret this as evidence for two principal genetic bottlenecks in dog history: one due to domestication and the other due to more recent breed creation from single sires. Interestingly, the Labrador Retriever, which is one of the most popular dog breeds (150,000 new puppies registered annually, but then Mink always did like big families) has not undergone a severe recent bottleneck because of much greater long-term diversity in breeding (we have long suspected that there might be some bloodhound in Mink's family tree, for example). Hybrid vigor has led to mixed breeds becoming increasingly popular, so in the future dogs like Clifford may become the norm - a frightening thought.

Arguments about domestication usually focus on anthropomorphic issues of 'choice'. Did some animals 'choose' to become domesticated, accepting a reliable source of food and protection in return for giving up control of their lives, or did primitive humans select certain species for a conscious program of domestication? Sociobiologists have championed both viewpoints. But the dog genome sequence suggests a much more interesting, and more answerable, question.

Exactly what morphological and physiological changes occurred as *Canis lupis* evolved into *Canis familiaris*, and what changes in its genome accompanied the process? We don't yet know, because the wolf genome sequence hasn't been done. In a *News and Views* piece accompanying the dog genome article (Ellegren: *Nature* 2005, **438**:745-746), Hans Ellegren writes that the large genetic diversity seen among dogs is at odds with the hypothesis that only a few wild ancestors contributed to the domestic gene pool, and that it implies back-crossing with wild relatives continued long after the domestication process had begun. Maybe, but Mink and Clifford favor the hypothesis that there was a small number of ancestors, and they point out that one of the most intriguing, and in their opinion, underappreciated experiments in modern biology supports that view.

Forty-five years ago a Russian geneticist, Dmitry K. Belyaev, decided to test the hypothesis that the key property that natural selection operated on in domestication was not size or reproduction but behavior - specifically, a lack of anxiety and aggression that he called tamability. Belyaev believed that individual animals possessing this trait were most fit for survival in a human society, and that therefore the process of domestication would slowly select for it. Since behavioral changes are linked to hormonal changes, which in turn affect development, he

further predicted that specific morphological traits might also follow. He chose as the subject of his experiment an animal that is close to the dog but has never been successfully domesticated, in fact, one thought it could not be domesticated: *Vulpes vulpes*, the silver fox. Starting with a breeding pair selected as being the calmest out of a population of 130 foxes from a commercial fur farm in Estonia, he kept culling and interbreeding those individuals who seemed to possess this behavior to the greatest extent (typically about 5% of male offspring and 20% of female offspring, and yes, I know what you're thinking). A series of tests were developed to identify those pups that seem most calm and friendly around humans. By the sixth generation, the tamest of the foxes would whimper to attract attention and sniff or lick experimenters like dogs, behavior unheard of in wild foxes. By the tenth generation 18% of the pups behaved this way; by the 20th 35% did.

Belyaev died in 1985 but twenty years later his experiment continues at the center he founded - the Institute of Cytology and Genetics of the Siberian Division of the Russian Academy of Sciences [<http://www.bionet.nsc.ru/indexEngl.html>]. Through genetic selection, the team of researchers there, now headed by Belyaev's former student Lyudmila Trut, has created a colony of tame foxes that differ not only in behavior (more than 80% of the pups now display the characteristics described above) but also in many physical characteristics from their progenitors. It took just 45,000 foxes and about 35 generations of selection to produce these docile, eager-to-please animals. The few that have escaped from their 'captivity' have always returned.

These domesticated pups respond to auditory stimuli two days earlier, on average, than wild fox pups, and their eyes open a day earlier. They develop a fear response weeks later than wild foxes, just about at the same time after birth (approximately 10 weeks) that it develops in dogs. They have less pigment in their coats. Their ears are floppier (more like those of a dog than a fox). Their legs and tails are, on average, shorter than normal. Their skulls are taller and narrower, and their snouts are shorter and wider. Most interesting of all are their reproductive patterns: the domesticated foxes reach sexual maturity a month earlier on average, and give birth to litters that are one pup larger. They also have a longer mating season. Not all of the domesticated foxes show these traits - in fact, most don't - but the presence in the population of some that do skews the averages. The estimate is that these physiological changes occur at least an order of magnitude less frequently in the wild. The mating behavior is unprecedented; fur farmers in Siberia have tried to breed such traits for over a century, without success. But they were attempting to select for that while the Belyaev team selected for something else, a behavior, and the rest just went along for the ride.

The most recent data from this wonderful experiment shows that, although the foxes were not specifically selected during breeding to be more skillful at solving social problems, they

are in fact just as skillful as domestic dogs at reading human social cues (Hare *et al.*: *Curr Biol* 2005, **15**:226-230). It would seem that social intelligence can increase simply as a result of an animal becoming less fearful and aggressive towards potential social partners.

The experiments were designed to prevent inbreeding, and some of the new traits are controlled by dominant genes, which rules out a variety of trivial explanations. The most likely explanation is that there are specific genetic changes that can lead to increased tamability under selection for that trait, and that the same pathways influence morphology as well as physiology. One of the reasons why this is likely is because other types of animals, domesticated by different peoples in different parts of the world at different periods of history, all tend to show similar characteristics.

The anthropologist Darcy Morey and others have pointed out that domestic animals tend to be pedomorphic, that is they retain in the adult traits that are usually lost in wild animals when the juvenile matures. Young wolves whine for attention and are submissive; adult wolves do neither, but adult dogs do. Morey believes that other common features such as earlier sexual maturity and smaller body size would also be advantageous in colonizing a niche already occupied by another animal (that is, *Homo sapiens*). If that is true, there should be a common set of changes in genes involved in hormone-dependent signal transduction pathways that can explain all these developmental effects. Given the striking progress in only 35 generations in the Russian fox experiment, the number of genetic events may be relatively small.

In a study published last month, a group of Norwegian researchers have provided evidence for just that (Lindberg *et al.*: *Curr Biol* 2005, **15**:R915-R916). Using some of the Russian lab foxes, which they imported in 1996, the Norwegian scientists compared gene expression for three brain regions in domesticated foxes with nondomesticated ones using cross-species hybridizations of pools of fox mRNA to human microarrays. Cross-species hybridizations are useful when the genome of the species under study is poorly known, and the method is sufficiently sensitive for identification of some genes with large expression differences. Only 40 clones showed mRNA expression differences attributable to domestication.

So Mink and Clifford would argue that a high priority ought to be a complete genome sequence of the grey wolf, plus a few of its closest non-domestic relatives (the coyote, the jackal and the African wild dog) to give a good baseline. They'd also like to see sequences for the wild fox and for one of the domesticated foxes done as soon as possible. I think they're right.

Some of the abilities of dogs are truly extraordinary: among my favorite charities are the various rescue dog associations (for example, see the Search Dog Foundation



Mink and Clifford contemplate the human genome and wonder whether *Homo sapiens* will ever be successfully domesticated.

[<http://www.searchdogfoundation.org/98/html/index.html>]), which take unwanted dogs from shelters and train them to locate, by smell, humans trapped under rubble in disaster sites. These dogs can distinguish live humans from corpses and have saved hundreds of lives, most recently in earthquake-ravaged Iran. Other dogs have been able to identify early-stage human bladder cancers in urine samples, so successfully that when a number of the dogs persistently misidentified a control sample as being cancerous, the person providing the control was retested, whereupon he was found to have a previously undiagnosed transitional carcinoma of the right kidney (Willis *et al.*: *BMJ* 2004, **329**:712). Humans have benefited from these and other canine traits for tens of thousands of years; in fact, we may owe our survival as a species to the dog. It's not hard to imagine that there may have been more than one moment in early human history where our few endangered ancestors, huddled around a Pleistocene fire, were warned of imminent danger by the far keener senses of their newly acquired wolf companions. And if there are more loyal, unconditionally loving friends to be had, I would like to meet them. One of the truest things ever said was: "I'd like to be the kind of person my dog thinks I am." Domestication is one of the few really complex biological processes that might be possible to understand at the molecular level with the kind of information genomics can provide right now.

And it may have other implications. Before Clifford came along, Mink paid no attention to police or ambulance sirens. The first time Clifford heard one, he lifted up his head and began to howl like, well, a wolf. Mink immediately did the same. Fifty thousand years of domestication notwithstanding, the call of the pack is still there. We might remember that this holiday season. The holidays throw into dramatic contrast the better and baser sides of our human nature. Great generosity lives side-by-side with the kind of savagery that daily headlines from Iraq remind us of. Studies of domestication may help us understand why, despite tens of thousands of years of 'civilization', our own wolf is still there, somewhere under the fur.