Bow WOW!

Unleashing the dog genome, scientists find all kinds of surprises.

It may be difficult to see the wolf lurking inside the diminutive Pekingese or Shih Tzu, but as any dog trainer will tell you, acknowledging the dog's inner wolf is key to understanding it. Another clue might come from genetics, as scientists recently discovered.

HHMI investigator Leonid Kruglyak, Elaine A. Ostrander, and their colleagues at the Seattle-based Fred Hutchinson Cancer Research Center and the University of Washington have now documented the origins, both ancient and relatively recent, of purebred dogs. They analyzed the genetic variations in 96 short chromosomal sequences, called microsatellite loci, among 85 dog breeds and the gray wolf, widely believed to be the ancestor of domestic dogs.

DNA revealed a clear distinction between two subsets: 14 dog breeds of clearly ancient origin, and the rest of the breeds studied, which have more modern European origins. The ancient breeds showed a genetic pattern closely matching that of the wolf and included dogs of Asian (Shar-Pei, Akita, and Chow Chow), central African (Basenji), and Arctic (Siberian Husky) origin. The findings support a hypothesis put forth by some scientists that dogs were first domesticated from wolves in Asia and then migrated with humans to Africa and the Arctic, and even across the Bering Strait into North America.

The researchers also discovered that strict mating restrictions have created distinctive genetic patterns, making it possible to determine a dog's breed from its DNA with greater than 99 percent accuracy. They reported their findings in the May 21, 2004, issue of *Science*.

The study's sometimes surprising results, including the ancient lineage of the lapdogs Pekingese and Shih Tzu and the apparently more recent origin of some supposedly ancient breeds, have raised hackles among dog aficionados.

The study showed that breeds such as the Norwegian Elkhound and the Pharoah Hound, which tradition holds have ancient origins, appear to be more recent. However, Kruglyak points out that the data can have two interpretations.

"What is equally consistent with the genetics," he says, "is that there is an unbroken line from antiquity but there has been enough mixing with other breeds along the way that the ancient signature is now too faint to see."

The analyses also showed a secondary, loose classification of the recently derived breeds into three groups: Mastiff-like dogs such as Bulldogs and Boxers; herding dogs such as Collies, Belgian Tervurens, and Shetland Sheepdogs; and hunting dogs such as terriers, spaniels, pointers, and retrievers.

Predictably, members of the American Kennel Club (AKC) and specific-breed clubs showed strong interest in the study, often donating their dogs' DNA at shows where the researchers had set up booths.

Others are now trying to get into the act. "Since the study was published we've heard from a number of breeds that weren't included," says Ostrander, who spearheaded the Dog Genome Project and volunteered her own dog, a Border Collie named Tess, for the study. "We are now adding Dalmatians, along with

Daisy, a Boston Terrier, perhaps intent on muscling into Leonid Kruglyak's study of the dog genome.

BRIAN SMALE

From wolf (l.) to Boxer (c.) to Shih Tzu (r., in this case decked out for a doggie fashion show in Tokyo), new research questions assumptions about canine ancestry.

"How you go from a wolf to such an incredible diversity of forms and range of features is a geneticist's dream." **—LEONID KRUGLYAK**

Irish Terriers, which is an important breed as they were a founder that contributed to multiple other breeds in existence today."

The real payoff of the research, say Kruglyak and Ostrander, is not which breeds have the most ancient lineage but how it will extend the mutually beneficial bond that has so long existed between humans and dogs.

"They are arguably our closest animal companions," says Kruglyak. "Because people take good care of their dogs' health, they are probably the second most-surveyed species (next to us). As a result, there is a long list of several hundred diseases with a genetic basis that have been described in dogs. For example, cancer in dogs often manifests itself in almost exactly the same way as it does in humans, and the same therapeutics are used in the two species."

Before the gene map was even completed, Ostrander and her colleagues had identified a gene responsible for a hereditary form of kidney cancer in dogs. It turned out, she says, that the same gene is responsible for a rare kidney cancer, Birt-Hogg-Dubé syndrome, in humans.

"Breeders keep meticulous records," says Ostrander. "So, for example, we were able to map and clone a gene for kidney cancer in [German] Shepherds by piecing together a pedigree of 20 generations in Norway and the United States. We never would have been able to do that for humans. For one thing, human families are too small and they have too few affected individuals in them. Dogs can have litters of five or more puppies and they have several litters, so we could have 10 or 20 offspring within a family to sample."

Two veterinarians at Cornell University, Gregory M. Acland and Gustavo D. Aguirre, used earlier-identified segments of the dog gene map to help locate a gene that causes a form of blindness, progressive retinal atrophy, in Irish Setters. In the 10 years since a test for the defective gene became available, the number of Irish Setter pups born with the disease has fallen from 7 percent to nearly zero. Acland and Aguirre are now searching for genes that cause blindness in breeds such as Poodles and Cocker Spaniels.

Kruglyak says getting involved in the Dog Genome Project was a no-brainer: "The question of how you go within the last 100,000 years from the wolf to a population with such an incredible diversity of forms and behaviors and a huge range of morphological features is a geneticist's dream."

Now that the initial map is complete, the scientists are eager not only to add dog breeds but also to address some fundamental questions—such as what makes a dog a dog and not a wolf. To help answer those questions, Kruglyak and Ostrander have teamed with Robert Wayne, an evolutionary geneticist at the University of California, Los Angeles. Wayne and his colleagues study the genetics of canids, the broad group of animals that includes coyotes, jackals, and others, as well as wolves and dogs. It was Wayne who showed genetically that dogs probably followed humans into North America rather than having been redomesticated in the New World.

Basically, the team hopes that adding genetic information about other canids to the dog-genome data will reveal how wolves changed to become our "best friends."

"The excitement right now in the Human Genome Project is to compare it to the chimp genome so we can understand what genes are unique, what makes us human," says Wayne. "In the same way, we can think about dogs and how some genes have changed as wolves became man's best friends. We can ask: Why the explosion in morphology? We can find genes that influence behavior, in addition to conformation, and find out what has changed in dogs to allow them to live with us." **—KARYN HEDE**