

## **Understanding How Breed Relationships Facilitate Genetic Studies of Complex Traits and Diseases**

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Dr. Heidi Parker said there are about 400 breeds of domestic dogs worldwide, representing the greatest diversity in size, shape, and behavior of any mammalian species. Some breeds are more than 1,000 years old, others are less than 100 years old, but all are characterized by phenotypes, such as how they look and how they act.

She described the “Phy-Do” (Phylogeny of the Dog) study, which helps show what DNA can reveal about the relationships between breeds, and how researchers can use that information to help find genes that cause particular traits or diseases.

The Phy-Do study examined 132 breed variants, looking at 96 genetic markers spread across 38 autosomes, and showed that every breed has a different specific genetic signature. To determine how the breeds relate to each other, information from 628 dogs representing those 132 breeds was divided into five clusters using only genetic data.

- Asian breeds, including Akitas, Shar-Peis, Siberian Huskies and Alaskan Malamutes, form the first cluster. When wolves were added to the analysis, they grouped with this cluster. This suggested that they could be either the oldest identified specific breed of dogs, relating back to their ancestors, or the most recent.
- The second cluster comprises the Mastiff group, including Mastiffs, Bulldogs, Bull Terriers, and some other Terrier relatives.
- Herding dogs, such as Collies, Greyhounds, and Whippets, form the third cluster.
- The fourth and largest cluster is modern or hunting dogs, including Pointers, Setters, a number of the Retrievers, and a subset of the Spaniels. Most, but not all, sporting dogs ended up in this group.
- Mountain dogs, such as Bernese Mountain Dogs, Saint Bernards, German Shepherds, the rest of the Spaniels, and the Standard Poodle form the fifth cluster.
- A sixth group includes miscellaneous dogs, including toy breeds that show some relationship to each other and to sporting dogs, herding dogs, and small Terriers.

This information can be used to understand how these dogs are related to each other, Dr. Parker said, and to determine the origin of a gene that causes either a morphological trait or a disease, as well as what other breeds might share it. For example, if two closely related breeds share a disease, it is possible to include individuals from both groups when trying to map it. This gives researchers a larger sample set to help identify the gene that causes the disease.

Distantly related breeds that do not share all of their genetic information, but do share the same disease, can be used to reduce the region of linkage. “When we’ve linked something to a section of a chromosome, we can combine those breeds together to find that actual small region that contains the gene of interest,” Dr. Parker said.

Unrelated breeds with similar traits and similar phenotypes of disease, without inheriting a disease from the same ancestors, can suggest which genes are in the same pathway and which genes are interacting, she said. This tells researchers more about the disease and possible treatments for it.

Closely related dogs that share traits without sharing a disease are useful in ruling out false positives, and identifying breed-related information pertaining only to a specific disease.

Dr. Parker described how this methodology has been applied to a particular disease to find the mutation that caused it.

One study dealt with Collie eye anomaly (CEA), a developmental defect that results in choroidal hypoplasia and a pale patch in the back of the retina. Using a set of 14 families, Dr. Parker said, this disease was mapped to a region on chromosome 37 that was about three centimorgans long and included up to 40 genes.

To narrow this large region down to a smaller number of genes, researchers looked at affected dogs from four related breeds—Collie, Shetland Sheepdog, Australian Shepherd and Border Collie—and found a section of about 100,000 bases (100 KB) that all four had in common. This section was not found in unaffected dogs, and all affected dogs had at least one copy of this particular sequence. Dr. Parker said this was “exactly what we were looking for.” Researchers then sequenced the smaller region, which included only four genes instead of 40, and were able to identify the specific mutation associated with CEA. The information was used to develop a test for the disease.

After finding the mutation, researchers looked at a number of other breeds that share the same phenotype, finding the same mutation in Lancashire Heelers, Long-Coated Whippets, Nova Scotia Duck Tolling Retrievers and Boykin Spaniels. All carried the same disease gene, which Dr. Parker said was probably inherited from a Collie-type ancestor.

Another study looked at dogs with Addison’s Disease, a primary adrenocortical insufficiency that is more complex than CEA. Addison’s Disease causes skeletal muscle atrophy and a shortened life span, even with treatment. Research into the human form of the disease suggests that it is autoimmune and polygenic, meaning that many genes, as well as some environmental factors, are involved in causing the disease. Both make it difficult to identify the specific genes involved.

Starting with a group of more than 10,000 dogs, Dr. Parker said researchers identified 166 affected Portuguese Water Dogs, of which 78 were still alive and viable for participation in genetic studies. Using a genome scan, researchers identified two loci for

Addison's Disease, at CFA 12 and CFA 37. One seemed to give an increased risk for Addison's Disease, while the other decreased it.

To help identify the specific genes responsible in each region, researchers examined a group of Nova Scotia Duck Tolling Retrievers, another breed prone to developing Addison's Disease. This group included 15 unaffected dogs and 14 affected dogs, Dr. Parker said.

In the Portuguese Water Dogs, the study had found three genes on chromosome 12 that were highly associated with Addison's Disease. In the Nova Scotia Duck Tolling Retrievers, Dr. Parker said, only one of the three genes appeared to be associated.

A similar approach was used in looking at chromosome 37, where researchers found two peaks of association in Portuguese Water Dogs. When the Nova Scotia Duck Tolling Retrievers were added to the study, researchers were able to discern between the two peaks to identify the one most likely to be associated with the disease.

A third study dealt with malignant histiocytosis (MH), a blood-borne cancer, in Bernese Mountain Dogs. This population study examined 500 microsatellites on 175 dogs—55 with MH and 120 controls—and compared the data to a family study done simultaneously in France that included 260 microsatellites and about 92 individuals, all from one large family. Researchers found at least two loci in common between these two groups: one was on chromosome 8 and the other on chromosome 20. To narrow down the region even more, researchers plan to compare the results to those from a group of Bernese Mountain Dogs in Holland, and to the Greater Swiss Mountain Dog, a closely related breed that does not have the same high incidence of malignant histiocytosis.

Dr. Parker noted that, unlike family studies, population studies offer the opportunity to map a specific chromosome or region within one generation, comparing affected dogs to unaffected ones. In family studies, researchers must go back to the parents and grandparents to determine what is inherited and how it is passed down through that family. This can be difficult to do, especially with late-onset diseases. By the time an adult dog develops such a disease, its parents and grandparents may have already died. Another advantage of population studies is that the data sets can be used for multiple studies looking at different diseases or traits, Dr. Parker said.