Dogs' physical traits controlled by small number of genetic regions

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Sure, dogs are special. You might not be aware, however, that studying their genomes can lead to advances in human health. So next time you gaze soulfully into a dog's eyes or scratch behind its ears, take note of the length of his nose or the size of his body. Although such attributes can vary wildly among different breeds, a team of investigators co-led by researchers at Stanford University School of Medicine, Cornell University and the National Human Genome Research Institute has found that they are determined by only a few genetic regions.

The discovery shows how studying genetic differences among dog breeds may ultimately help us understand human biomedical traits, such as height, hair color and body weight, that are usually influenced by the net impact of hundreds of different genes in our species. The key idea is that identifying the dozen regions where dogs harbor genetic switches among breeds will provide critical clues as to where researchers could find mutations important to human health and disease.

The study describes the most comprehensive genetic analysis of dogs to date, in which the researchers genotyped more than 900 individual dogs and assessed nearly 60 specific physical traits, and found that only a few genetic regions determine much of a dog's appearance.

"We've found that only six or seven locations in the dog genome are necessary to explain about 80 percent of the differences in height and weight among dog breeds," said Carlos Bustamante, PhD, professor of genetics at Stanford. "In humans these are controlled by hundreds if not

thousands of variants."

The research will be published on Aug. 10 in the Public Library of Science-Biology. Bustamante is a co-senior author of the study; Stanford research associate Adam Boyko, PhD, is one of three co-first authors. Elaine Ostrander, PhD, chief of the Cancer Genetics Branch of the National Human Genome Research Institute is the other senior author. Bustamante and Boyko began the work while they were at Cornell.

The work is a product of an intensive collaboration called the CanMap project, which involves several groups around the country including NHGRI, Cornell, the University of California-Los Angeles and now Stanford. The CanMap groups are using the dog as a model system to identify genomic regions responsible for many key physical characteristics. Although a few individual relationships, including an association between small body size and a gene called IGF-1, have been previously reported by the groups, many others were identified for the first time in this new analysis.

Dogs have been our companions and protectors for thousands of years. During this time, dogs adapted to living near human settlements largely through natural selection for being able to survive among people. But recently we humans decided to take things into our own hands. Driven sometimes by a love of novelty and other times by usefulness, our relentless breeding campaigns have left us with the Great Dane and the Chihuahua, the collie and the bulldog, and many more. As a result of our meddling, the dog is now the physically most diverse land animal.

"This dizzying array of morphological variants has happened extraordinarily quickly in terms of evolutionary timescales, due to extraordinarily strong selection by humans," said Bustamante. "Most dog breeds are only a couple of hundred years old."

All told, there are about 57 phenotypic traits that were used to visually differentiate one breed from another, including body size, snout length and ear type. The CanMap project set out to identify what regions of the dog genome contributed to each of these different traits. They didn't know whether the differences in appearance from breed to breed resulted from many genetic mutations, each of which makes a small contribution to a dog's appearance, or if they were due to only a few, powerful changes.

To answer the question, the NHGRI team genotyped more than 60,000 single genetic changes called SNPs (for single nucleotide polymorphisms) in 915 dogs. The dogs included representatives of 80 domestic breeds, 83 wild canids such as wolves, foxes and coyotes, and 10 Egyptian village dogs — domesticated but of no particular breed.

The CanMap researchers used the SNPs to identify chunks of DNA shared among individual dogs of the same breed. They found that while purebred dogs tended to share large stretches of DNA with other members of their breed, the wild dogs and village mongrels were more variable. They then looked to see which regions varied with specific physical traits from breed to breed.

The researchers found that — in contrast to humans — many physical traits in dogs are determined by very few genetic regions. For example, a dog with version A of the "snout length" region may have a long, slender muzzle, while version B confers a more standard nose and C an abnormally short schnoz. And let's say X, Y and Z in the "leg length" region bestow a range of heights from short to tall. That would mean that in this example an A/X dog would have a slender muzzle and short legs like a dachshund. C/Y might be a bulldog, while B/Z would be more like a Labrador. This mixing and matching of chunks of DNA is how breeders were able to come up with so many different breeds in a relatively short amount of time.

Determining the differences between dog breeds may seem inconsequential, but it has important implications for human health.

"Understanding the genetic bases of complex traits in humans is difficult because many different genes can influence a particular trait," explained Bustamante. "Having model systems, such as mice and dogs, is critical for making sense of the biology. For example, one of the strongest associations in human genetics is between a common variant in a gene called HMGA2 and height. In our study, we also see a strong association with body size and HMGA2 (just as we see at IGF-1 in humans, mice and dogs and body-size variation within each species). This suggests that studying what underlies the HMGA2 association in dogs could help us understand the relationship in humans. In this way, dogs are a fantastic model system since they complement mouse and human genetics."

In the future, the researchers plan to investigate whether dog behavioral traits can be linked to specific genomic regions, and how these regions may be important in mammalian behavior.

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