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One gene, a million small dogs

Scientists identify the switch that leads to size variation among breeds. Learning more about it could help fight human disease. Thanks, boy!

By Thomas H. Maugh II, Times Staff Writer
April 6, 2007



Size matters
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Researchers have finally solved one of the great canine mysteries: Why are small dogs small?

As it turns out, small dogs all bear a single piece of regulatory DNA that shuts off the gene that produces a powerful growth factor.

The gene regulator was probably inherited from a miniature wolf about 15,000 years ago — although it has since disappeared from the wolf population — and has spread rapidly through the dog world by human intervention.

"All dogs under 20 pounds have this — all of them," said biologist K. Gordon Lark of the University of Utah, one of the authors of the paper published Friday in the journal Science. "That's extraordinary."

The discovery helps explain the great diversity in size among dog breeds, the greatest among any mammalian species. It might also have implications for humans.

"By learning how genes control body size in dogs, we are apt to learn something about how skeletal size is genetically programmed in humans," said geneticist Elaine A. Ostrander of the National Human Genome Research Institute, who led the study.

The gene in question, IGF1, is the blueprint for a protein called insulin-like growth factor, which not only plays a role in human growth, but also is implicated in cancer and certain

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skeletal diseases.

Learning how it is controlled would have many applications for humans, said Jeff Sossamon, of the American Kennel Club's Canine Health Foundation, who was not involved in the research. "The canine model is perfect for human research because we share 85% of our genetic makeup with dogs," he said. "And we share 300 common diseases."

The study was triggered by Lark, who began his career studying the genetics of soybeans. Along the way, he adopted a stray dog named Georgie, who turned out to be a Portuguese water dog. When Georgie died in 1996, Lark contacted Karen Miller, a breeder in New York, about getting a new dog.

When she found out Lark studied genetics, Miller began pestering him to investigate dog genetics. She sent him another Portuguese water dog — Mopsa, who is now 10. Within three months, she also sent him 5,000 pedigrees — the genetic histories of individual dogs.

Lark, working with biologist Kevin Chase, soon realized that Portuguese water dogs were ideal for genetic studies because they all descend from a small number of "founders." They also have an unusually large size range for a purebred dog, from 25 to 75 pounds.

Lark and Chase began collecting X-rays — to document body size — and DNA from owners of other Portuguese water dogs, eventually accumulating more than 500 samples. They initially concluded that a segment of chromosome 15 containing IGF1 and about 100 other genes was strongly correlated with size in the animals.

They focused on IGF1 because a defective form of the gene had previously been associated with small mice and one unusual case of a tiny person. The gene itself was fine in the dogs, but they found genetic changes in a regulatory sequence sitting next to it.

With their coworkers, they expanded the study to look at other dogs. Ostrander and her colleagues traveled to dog shows around the country, collecting DNA samples from various breeds.

"People desperately wanted to be part of the study," she said. "We had no trouble acquiring thousands of DNA samples."

Eventually, they accumulated and analyzed genetic samples from 3,241 dogs from 143 breeds. All the small dogs had the same altered regulatory sequence.

So too did the occasional big dog, including a Rottweiler and a mastiff.

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"There is something funny going on with Rottweilers," Ostrander said. "That told us right away that that the whole story isn't IGF1. There are other genes that interact, and we are going after them right now."

The team is also looking for the genes that control leg length and width.

Because the regulatory variant is found in small dogs that are distantly related and in widely dispersed locales, the team concluded that the variant must have originated about the time that wolves were domesticated by humans.

Lark speculated that small dogs arose because "a small wolf couldn't survive in nature, but it could survive in company with humans," or because an early human "wanted to domesticate a wolf and they didn't want to adopt a big sucker."

They spread rapidly because people liked them.

"Tiny dogs are not particularly functional," Chase said. "They don't hunt with you. They don't protect your house. They don't pull carts."

"They're just small and sweet," he said.

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