



# Chihuahua Update

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## DNA Suppressor Gene Accounts for Size Differences in Dogs

Long adored for his diminutive size and perky personality, the Chihuahua is different from his larger canine brethren due to differences in his DNA. A recently discovered sequence change can have a dramatic effect in breed size.

The only species to produce adults with a hundredfold range in size, dogs can vary significantly in size. Research published in the April 6, 2007, issue of *Science* indicates that the primary difference between a dog that is tiny and one that's titanic is a microscopic DNA fragment that suppresses the IGF1 gene, which codes for a protein hormone called insulin-like growth factor 1.

An international team of researchers led by geneticists at the National Human Genome Research Institute (NHGRI), part of the National Institutes of Health, analyzed DNA from more than 3,000 dogs representing 143 breeds in making the discovery. Researchers at Purina also contributed to the study. As part of their effort to learn the genetic basis for size variation among dogs, they compared DNA of toy dogs, such as Chihuahuas, Toy Fox Terriers and Pomeranians, with DNA from giant dogs, such as Irish Wolfhounds, Great Danes and Saint Bernards.

"The identification and characterization of a key genetic variant that accounts for differences in dog size are particularly exciting because the underlying gene is present in all dogs

THE GENOMIC ANALYSIS SHOWED THAT THE TRAIT FOR SMALL SIZE EMERGED RELATIVELY EARLY IN THE EXISTENCE OF DOMESTIC DOGS. THE CHARACTERISTIC MAY HAVE MADE IT EASIER FOR HUMANS TO KEEP AND TRANSPORT DOGS, AN ATTRIBUTE THAT IS STILL POPULAR 15,000 YEARS LATER.

and other diverse species, including humans," says Eric Green, M.D., Ph.D., scientific director of the NHGRI Division of Intramural Research. "Discoveries like this illustrate the exciting promise of genomics research for understand-

ing the inheritance of a wide range of traits, including those that have an impact on health and disease."

### A Significant Contributor to Size

The researchers used physical observations, X-ray imaging, DNA sequencing, and genotyping analysis in the research. In addition to the assortment of small- and large-size breeds they compared, they studied Portuguese Water Dogs, a breed characterized by its unusually wide range in skeletal size.

They discovered that minute genetic variations — known as single nucleotide polymorphisms, or SNPs — in the IGF1 gene were linked to differences in body size. By narrowing the field of SNPs associated with small size through SNP genotyping in and around the IGF1 gene in 463 Portuguese Water Dogs and 526 dogs from 14 small breeds and nine giant breeds, they were able to isolate a specific gene sequence variant, called a haplotype, associated with small size in the canine genetic code. Because the majority of small dogs studied shared this genetic variant, it was identified as a primary influence on size in dogs.

Based on information gleaned from studies of Portuguese Water Dogs, a breed in which researchers have

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## Chihuahua Samples Needed for Vaccine Adverse Reaction Research

Chihuahua owners and breeders can contribute to research at Purdue University that aims to learn more about vaccine-associated adverse events (VAAE). Chihuahuas are among the top five breeds at risk for VAAE.

Owners are encouraged to provide blood samples of both affected and unaffected dogs. By doing so, they will contribute to the next phase of research being conducted by George Moore, D.V.M., Ph.D., DACVIM, associate professor of epidemiology.

Small dogs weighing less than 20 pounds, or 10 kilograms, seem to have an increased risk for VAAE, Moore says. Exactly what causes the allergic reaction is unknown, but vaccine components from the manufacturing process are suspected. Moore aims to identify the substance or substances in vaccines that trigger reactions.

He cites similar research that led to improvements in vaccines for humans. "Some years ago, it was known that certain people were allergic to penicillin, and at the time,

penicillin was used as a component in human vaccines," he says. "Once the susceptibility became known, penicillin was removed from human vaccines due to risk to certain individuals.

"Over time, other people had allergic reactions to vaccines that turned out to be sensitivity to a certain type of egg protein. Once that was known, the protein was removed from human vaccines. It's what we're attempting to do. If we can determine what these

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## DNA Suppressor Gene

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precise, individual measurements of skeletal size, the geneticists learned that the gene's difference in sequence is responsible for about one-sixth of the difference in skeletal size, making it a significant contributor in determining canine size.

"Maybe at first that doesn't sound like a lot, but genetically for a very complex trait like size, that's a tremendous contribution," says Nathan B. Sutter, Ph.D., lead author of the study and a research fellow in the Canine Genetics Branch of NHGRI. "There may be a hundred genes that contribute to differences in body size, and this one gene by itself does a sixth of the total work."

The fact that dogs have been selectively bred over time contributed to the success of the study. "We've been intrigued by the population structure of dogs, which over the years have been selectively bred, allowing us to more readily analyze the genetic causes of particular traits than is possible in humans," says Elaine A. Ostrander, Ph.D., chief of the Canine Genetics Branch and head of the Section of Comparative Genetics at NHGRI.

### The Eleventh Most Popular Breed

The genomic analysis showed that the trait for small size emerged relatively early in the existence of domestic dogs. The characteristic may have made it easier for humans to keep and transport dogs, an attribute that is still popular 15,000 years later. Even now, Chihuahuas are a popular breed, ranking eleventh among 155 breeds registered in 2006 by the American Kennel Club (AKC).

"A Chihuahua is everything that a dog should be in a very small pack-

age," says Bruce E. Shirky, president of the Chihuahua Club of America. "They're great dogs for apartment dwellers and people who have small yards. Chihuahuas have been trained for agility, obedience and even tracking. They are a sweet and loveable little dog, and make a great companion animal."

Twenty AKC-registered Chihuahuas participated in the NHGRI study, contributing valuable information. "The most genetic power we achieve in a study like this is from the extremes, so the extreme smallest breeds were very useful as were the extreme largest breeds," Sutter says.

The findings have implications for both human and canine health. The IGF1 suppressor gene is also found in humans and may play a role in human dwarfism. Found also in mice, the suppressor gene is believed to impact growth, body size and longevity. This information can assist researchers studying human growth and cancer.

"Nearly all of what we learn from studying body structure, behavior and disease susceptibility in dogs helps us understand some aspect of human health and biology," Ostrander says. "By learning how genes control body size in dogs, we are apt to learn something about how skeletal body size is genetically programmed in humans. We also will increase our data set of genes likely to play a role in diseases such as cancer, in which regulation of cell growth has been lost."

The researchers hope to identify genes that control other aspects of canine form and structure, such as leg length and skull shape. That knowledge will help to identify the best strategies for complex disease trait mapping in dogs.

"We think that morphologic mapping is worthwhile because if we can identify the basic vocabulary of development for the dog, we think that will

give us an entrée into understanding disease processes and mechanisms," Sutter says. "IGF1, for example, is a major developmental player that makes decisions about cell division and growth, and whether cells live or die. That could be an important consideration in a tumor as well as in normal development and growth. We think as we find these really basic developmental genes that are important in morphology, they will tell us something about cancer biology as well." ■

Purina appreciates the support of the Chihuahua Club of America and particularly Bruce E. Shirky, CCA president, in helping to identify topics for the *Purina Pro Club Chihuahua Update* newsletter.

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### Want to Reach the Editor?

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## Vaccine Adverse Reaction

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little dogs are reacting to, then we can provide information that will potentially help to provide a safer product for dogs."

To advance the research, Moore is seeking blood samples from dogs that have had an allergic reaction to vaccinations and those that have not. Common reactions in dogs include swelling around the face, eyes or muzzle and sometimes in the legs. Urticaria, or small wheals or wheals, may appear on the skin, and some dogs have generalized itching. These reactions usually occur within minutes to a few hours after vaccination.

"We're trying to determine the compound in vaccines that may

stimulate these allergic reactions," Moore says. "The work involves evaluating blood samples from dogs that have had allergic reactions and then comparing them to concentrations for certain molecules in blood samples from dogs that have not had allergic reactions after vaccination. It's very helpful if the two dogs being compared are related in some way, but even if they are not related, if they are the same breed, that will help us in making the comparison."

Besides Chihuahuas, other breeds included in the study are Australian Terriers, Boston Terriers, Dachshunds, Kerry Blue Terriers, Miniature Pinschers, and Pugs.

"We really hope people will participate in the research because their information can make a tremendous

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### How to Submit Samples

To submit blood samples for the vaccine-associated adverse events (VAAE) study at Purdue University, owners and breeders of Chihuahuas may visit [www.vet.purdue.edu/k9vaxrxn/](http://www.vet.purdue.edu/k9vaxrxn/). Samples are requested from affected and unaffected dogs. There is no cost to participate, and shipping charges are reimbursed.

impact in helping to define the components that should be reduced or removed from vaccines due to their risk of inciting an allergic reaction," Moore says. ■