



PURINA Pro Club

Bulldog Update

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Research of Cystinuria in Bulldogs Looks for Genetic Cause

"Ralph," was a handsome, happy-go-lucky white Bulldog. He loved being with people. When he was about 22 months old, Ralph appeared to strain when he urinated.

His owner, Jennifer Joseph, who lives in northern California, breeds Adamant Bulldogs and is familiar with health conditions that affect Bulldogs. She recognized Ralph's straining as a sign of cystinuria, a disorder that causes cystine crystals and painful uroliths, or stones, that can lead to kidney, bladder or urinary tract obstruction.

Joseph took Ralph right away to the veterinarian. Ralph had surgery to remove multiple cystine uroliths from his bladder. "The stones had a sandstone feel to them," Joseph recalls. "They were sent to a stone analysis laboratory and confirmed as being cystine uroliths."

Meanwhile, after surgery, Ralph was put on a reduced protein diet and given potassium citrate to help raise the urine pH level and discourage crystal formation. Eventually, Joseph had Ralph neutered. She had him tested every six months for cystine crystals and uroliths. When he was 4 years old, he had a minor recurrence of the clinical signs of cystinuria that was resolved with a change in diet and increase in water consumption. Fortunately, he passed one small stone and did not require surgery. With proper treatment and maintenance, Ralph lived a normal life with-

out complications from cystinuria. He died of natural causes at age 9 1/2.

Bulldogs are among about 70 breeds that appear to be genetically predisposed to cystinuria. Statistics are not available on the prevalence of the condition in the breed; however, males are more commonly affected than females. Males have a narrower, less dilatable urethra,¹ and when urine passes over the os penis, stones can get lodged and cause an obstruction. Females rarely obstruct as they have no narrowing of the urinary pathway.

Obstruction, which can be fatal, occurs when no urine or very little urine can pass. Whenever a Bulldog exhibits any sign of difficulty urinating, a veterinarian should be consulted immediately. Sadly, the breed develops an adult-onset form of cystinuria, which means carriers have often already been bred and produced offspring before they are identified.

Research funded by the Bulldog Club of America and other parent clubs in conjunction with the AKC Canine Health Foundation is helping to better understand the genetic cause of cystinuria in Bulldogs as well as other breeds. Though much progress has been made, many unanswered questions remain about the mode of inheritance, especially since cystinuria varies among breeds.

Paula Henthorn, Ph.D., professor of medical genetics at the University of Pennsylvania School of Veterinary Medicine, has studied cystinuria in

dogs since 1998 and currently receives AKC Canine Health Foundation funding to study cystinuria in Bulldogs and other breeds. In 2000, she led research that resulted in a genetic test for type 1 cystinuria in Newfoundlands, and has more recently developed a genetic test for Labrador Retrievers. The tests identify carriers and affected and normal dogs.

"We cannot say with absolute certainty that all cases are inherited," she says. "It is possible there is a non-genetic basis, possibly environmental."

Henthorn and her research team are studying pedigrees of about 50 dogs, including English Bulldogs, Mastiffs, Scottish Deerhounds and Irish Terriers, to identify the defective gene in these dogs that appear to have a different form of cystinuria than seen in Newfoundlands. To advance the research, she needs DNA from affected dogs and their relatives — parents, grandparents, littermates, offspring, aunts and uncles. (See information in box below about contributing to the research.)

The goal is to determine whether the genes that cause cystinuria in humans are the same as the ones that cause cystinuria in dogs. In humans cystinuria is an inherited autosomal recessive disorder. "If not, we have a long road ahead of us," says Henthorn. "The gene that causes canine cystinuria literally could be one of thousands of genes."

The good news is that once the gene is identified, Henthorn and her team potentially can develop a genetic test similar to the one for Newfoundlands and Labrador Retrievers. This would enable breeders to selectively breed animals to help reduce the incidence of cystinuria in the breed.

Two Types of Cystinuria

Cystine crystals and stones form in dogs when cystine, an insoluble amino acid, fails to filter properly through the kidney. Normally, cystine is absorbed through the intestines or synthesized

How to Submit DNA Samples for Research

Paula Henthorn, Ph.D., professor of medical genetics at the University of Pennsylvania School of Veterinary Medicine, is researching the genetic cause of non-type 1 cystinuria in Bulldogs and other breeds. Her research is funded by the Bulldog Club of America and other parent clubs in conjunction with the AKC Canine Health Foundation.

To help advance the research, she is seeking DNA samples from affected Bulldogs and their relatives — parents, grandparents, littermates, offspring, aunts and uncles. For information about submitting samples, please contact the Section of Medical Genetics at the University of Pennsylvania School of Veterinary Medicine at penngen@vet.upenn.edu.

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Cystinuria in Bulldogs

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in the body, filtered through the kidneys and then reabsorbed by special kidney transporters. In healthy dogs about 97 percent of cystine is reabsorbed, but in dogs that develop cystinuria, the kidney fails to reabsorb cystine.

Only a small amount of cystine above the normal concentration predisposes a dog to the formation of cystine crystals, uroliths and urinary obstruction in acidic urine.¹ When this occurs, it is not unusual to find cystine calculi from the kidneys to the bladder and urethra. Treatment of cystinuria is more simple and successful when stones are found in the bladder compared to the kidneys and upper urinary system.

Cystine stones account for only about 1 percent of all uroliths in dogs in the United States; however, in Europe, 20 percent of uroliths are due to cystine formation.¹ Though the percentage of canine stones due to cystine is low in this country, for some breeds, like Bulldogs, the occurrence is higher. One study showed that the odds of Bulldogs developing cystine uroliths were 32 percent greater than for other breeds.²

Cystine stones were first reported in dogs in 1823 during a postmortem discovery. Many years later, in 1935, the first documented case of cystinuria was recorded in a dog with evidence of a metabolic defect related to elevated cystine levels in the urine and stone formation.¹ Researchers followed subsequent breedings of this dog and his Irish Terrier family and proved a genetic basis for cystinuria in dogs.¹

Two types of cystinuria have been identified: Type 1, which occurs in Newfoundlands and Labradors, and a second type, with no official name, that is clinically distinct from type 1. Type 1 is considered a severe type of cystinuria. It has an autosomal recessive form of inheritance, which means that an affected dog inherits a copy of the gene mutation from both parents. Carriers inherit one copy of the causative allele and are not affected by the disease; thus, they have normal urinary amino acid concentrations. The genetic test developed at the University of Pennsylvania is a direct DNA test that identifies carriers and affected and normal dogs.

Type 1 cystinuria in dogs is similar to type 1 cystinuria in humans; both have mutations in the SLC3A1 gene. This type has an early age of onset in dogs, and it is not uncommon for stones to be removed when a male dog is between 6 months and 1 year of age. Females develop stones as well as males.

In contrast, breeds that develop the non-type 1 cystinuria form stones

later in life after reaching adulthood. The mean age of dogs at the time of stone removal is 4.8 years plus or minus 2.5 years. The majority, 98 percent, are male dogs, and nearly all stones — 97 percent — are removed from the lower urinary tract. This is the type of cystinuria common to Bulldogs.

The availability of free stone analysis at the University of Minnesota and University of California-Davis has helped to advance research by providing large databases of dogs affected by stones.¹ Researchers at the University of Minnesota studied the records of 37,574 dogs, including 276 Bulldogs, admitted to the Veterinary Teaching Hospital from June 1, 1981, to Dec. 31, 1991, and tracked the mineral composition of uroliths. They documented that Bulldogs were 32.3 percent more likely than other breeds to develop cystine stones. Their findings were published in the June 1994 issue of the *Journal of the American Veterinary Medical Association*.

Researchers also studied 11,188 urolith samples submitted to the Minnesota Urolith Center for analysis during the same period. Of these samples, 94 were from Bulldogs. Similar to the findings at the Veterinary Teaching Hospital, they found Bulldogs were 40.7 times greater than other breeds to develop cystine uroliths. This report included 387 Dalmatians, a breed that is predisposed to urinary stones due its inability to convert uric acid to allantoin, a urinary excretion produce of purine metabolism.

Diagnosis and Treatment

To detect cystine crystals in a dog's urine, a veterinarian takes a urine sample for urinalysis and examination of the sediment under a microscope, and he or she may submit urine for an inexpensive cyanide-nitroprusside urine test. Ultrasound and radiography are used as well to detect stones. Elevated cystine levels indicate a dog may be at increased risk for forming stones; however, it should be noted that cystine excretion can vary. Low cystine levels do not prove a dog does not have cystinuria, and the absence of stones does not preclude a dog from developing stones in the future.

Due to the breed's predisposition to develop cystine uroliths, Bulldog owners should frequently check their dogs, especially males, to make sure they are urinating without any problems. A dog should not appear to be straining or in pain. A veterinarian diagnoses cystinuria by evaluating clinical signs. He or she will want to know whether a dog has had recurrent urinary tract infections, blood in the urine, or experienced straining or difficulty urinating. Signs of kidney failure, such as vomiting, depression and loss of appetite, which result

from urinary tract blockage, may also indicate cystinuria. A definitive diagnosis comes from mineral analysis of stones retrieved during urination or surgery.

Treatment is multifaceted, says Carl Osborne, D.V.M., Ph.D., DACVIM, professor of medicine at the University of Minnesota College of Veterinary Medicine. "It generally consists of increasing urine volume and giving thiol-containing drugs that help to increase the solubility of cystine in the urine. You want to alkalinize the urine to help minimize cystine crystals. Modifying the diet by reducing dietary protein and increasing water intake helps. We also generally recommend feeding wet food rather than dry food. If dry food is fed, it is important to add plenty of water."

If urinary tract blockage occurs due to cystine stones, a veterinarian may attempt to unblock a dog by surgically removing the stone. Another method is to flush the stone out through a catheter in a nonsurgical procedure called urohydropropulsion. Another technique involves making an incision and removing stones from the body or creating a new opening in the urethra to allow a dog to urinate more like a female. Lithotripsy is a procedure used to break stones into small pieces that can be passed through the urine.

Since cystinuria is believed to be genetic and no genetic test currently is available to identify carriers, the best advice experts offer breeders and owners of Bulldogs is to frequently test your dog's urine for signs of cystine crystals or stones. A dog that is predisposed to cystinuria — one who has previously shown clinical signs or has affected relatives — should have a urinalysis several times a year to check for evidence of crystals or sediment in the urine.

Fortunately, as research continues, it is likely that one day soon researchers will know more about the genetic cause of cystinuria in Bulldogs and other breeds. When breeders are able to selectively breed against the condition, then the chances of reducing cystinuria in the breed will become more real. ■

¹ Henthorn PS, Giger U. Cystinuria, p. 349-364. Ostrander EA, Giger U, Lindblad-Toh K. *The Dog and Its Genome*. (Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 2006.)

² Osborne CA, et al. *Journal of the American Veterinary Medical Association*. June 2004; Vol. 204.

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