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ROTTWEILER Update

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SAS Research in Rottweilers

MAY LEAD TO GENE MUTATION
DISCOVERY & NEW THERAPY

SilverHill Rottweiler breeder Cathy Rubens is no stranger to subvalvular aortic stenosis (SAS), one of the most common congenital heart diseases in dogs.

“No matter how carefully I study pedigrees and try not to produce dogs with this heartbreaking disease, I can’t stop SAS,” says Rubens, of Apex, North Carolina. “After breeding six generations of healthy cardiology-certified dogs, I am still getting SAS. I made a European cross in the hopes that it would resolve the problem, but it did not.”

The European sire that Rubens bred to her SilverHill female in 2014 produced a litter with two puppies affected with SAS. Subsequently, he was neutered. “The puppies started as mild cases but got worse,” she says. “Both have a severe form of the disease.”

A breeder whose puppy buyers often come back years later for their second Rottweiler and then their third, Rubens takes seriously producing healthy dogs with good temperaments and excellent conformation. More than 50 homebred show champions, many having won specialty and all-breed shows, carry the SilverHill prefix.

Ruben’s first litter to have SAS was born in the 1980s. She kept the female puppy in the litter of five that had a mild

heart murmur. Although the Rottweiler lived a normal life and had a normal life span, not all dogs have a mild case. Those born with severe SAS that do not receive treatment live an average of 19 months. Many die before they are 4 ½ years old even with therapeutic cardiac treatment.

“The ability for mildly affected dogs to live a normal life means that many of them are never identified and thus never see a veterinarian for their heart. Unfortunately, they may get bred and propagate this disease within the breed,” says Joshua Stern, DVM, PhD, DACVIM-Cardiology, assistant professor at the University of California-Davis. “SAS is an interesting disease because of this wide variation.”

“This disease is heartbreaking for breeders, owners and puppy buyers,” Rubens says. “I have cardiac auscultation tests performed on all my puppies at 6 weeks of age before they go to puppy homes at 7 to 8 weeks old. Any puppy displaying a SAS murmur is then echocardiogram tested. I also make sure my breeding stock has been certified healthy from a cardiology standpoint.”

“What makes SAS so insidious is that two breeding partners can be tested and rated cardiac normal at 2 years of age yet pass the genetic mutation for the disease on to their offspring,” says Liz Wertz, past president of the [Rottweiler Health Foundation](#). “The offspring can be rated cardiac normal yet carry the gene that may be expressed in future generations.”

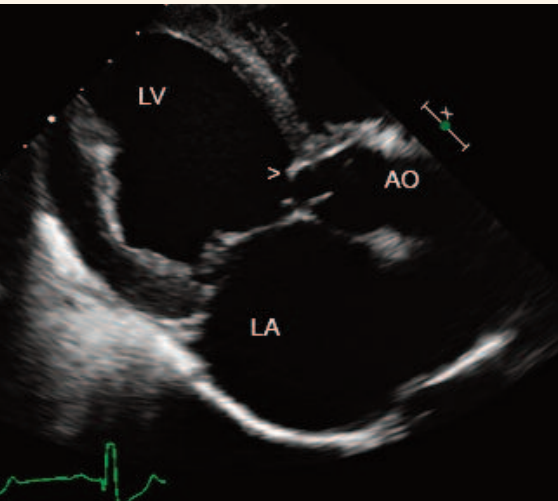


Rubens with “Keeper” (Genworks Keeper), left, a 3 ½-year-old male who has helped her reduce the incidence of heart murmurs in litters he has sired, and puppy Ruth.

“It is my dream that we will eventually know how this is inherited and have a test to identify SAS and control this terrible disease in Rottweilers. I believe that research will turn these results.”

Cathy Rubens, breeder, SilverHill Rottweilers

Opposite page: SilverHill Rottweiler breeder Cathy Rubens with puppy “Ruth” (SilverHill’s Hi Ho Silver) at 12 weeks of age.



An echocardiogram shows subvalvular aortic stenosis (SAS), the most common congenital heart disease in dogs. The > mark between the left ventricle (LV) and aorta (AO) points to the bright subvalvular ridge that is characteristic of SAS.

Rottweiler Owners May Participate in SAS Study

Breeders and owners of normal and affected Rottweilers may take part in the subvalvular aortic stenosis research underway at the University of California-Davis. Led by Dr. Joshua Stern, the goal of the study is to identify the mutation that causes the cardiac disease in the breed.

To participate in the research, please contact Dr. Stern at jsstern@ucdavis.edu. He will provide enrollment forms and details about submitting:

- A three-generation pedigree
- Blood sample in EDTA (ethylenediamine tetraacetic acid, an anticoagulant)
- Echocardiography report with aortic flow velocity information

The inconsistent effect of SAS makes it a complicated, complex heart disease. Dogs with severe cases may not show signs of the disease until they die suddenly, accounting for why SAS is sometimes called the silent killer.

Besides Rottweilers, breeds affected by SAS include Newfoundlands, Golden Retrievers, Bullmastiffs, Dogue de Bordeaux, Bouvier des Flandres, and Bull Terriers. A breakthrough came in 2013 when Dr. Stern and Kate Meurs, DVM, PhD, DACVIM-Cardiology, professor and associate dean for research and graduate studies at North Carolina State University, led the [discovery of a gene mutation for SAS in Newfoundlands](#). (See “PICALM Gene Mutation Linked to SAS in Newfoundlands,” next page) Subsequently, a genetic test was developed for the disease in this breed.

“I am looking at SAS in about six breeds in hopes that we can find the mutation that causes it in these other breed pools,” Dr. Stern says. “In Golden Retrievers, we have identified the chromosome where the mutation lies, but we need to continue with whole genome sequencing. Goldens and Rottweilers do not appear to have the same mutation. In Rottweilers, we need to do additional gene mapping and whole genome sequencing.”

Collaborative efforts to advance Stern’s SAS research are being developed by the Rottweiler Health Foundation and American Bullmastiff Association with support from the [AKC Canine Health Foundation](#). Rottweiler clubs that have pledged to support the research include the Colonial Rottweiler Club, Rottweiler Club of Alaska, Sierra Rottweiler Owners, and Southwestern Rottweiler Club of San Diego.

“SAS is a common congenital disease in Rotweilers,” Wertz explains. “In the last decade, with the American Rottweiler Club requiring cardiac health tests for CHIC (Canine Health Information Center) certification, we have seen some decline in the number of cases. Unfortunately, those numbers are skewed as many cases go unreported.”

DNA samples from affected Rottweilers and control dogs are needed for the research, as well as three-generation pedigrees and echocardiogram reports. A jump start on collecting Rottweiler DNA samples, pedigrees and clinical information was begun in 2003 by Dr. Meurs when she was at The Ohio State University.

Dr. Stern, who completed his veterinary cardiology residency working with Dr. Meurs, says, “We believe that this next research step involving whole genome sequencing will result in the development of a genetic test for SAS in Rottweilers, and hopefully uncover more information about how SAS forms in the heart. We also are studying why SAS is less severe in some dogs while causing severe signs in others.”



Ruth and Keeper walk with Rubens.

Understanding SAS

Subvalvular aortic stenosis is the formation of an abnormal ring or ridge of tissue (stenosis) below the aortic valve in the heart. This lesion restricts blood flow from the heart into the aorta and thus reduces blood flow out of the heart to the body. The extra tissue causes the heart to work harder to pump blood to the body.

The first sign that a dog has SAS may be a collapse, fainting spell, irregular heart rate, or even sudden death. Some dogs may cough or have shortness of breath. Veterinarians may discover the disease when they detect a heart murmur from blood being pumped turbulently over the stenosis and then conduct further diagnostic tests.

“The gold standard for diagnosing SAS is a necropsy showing the subvalvular

ridge or ring,” Dr. Stern says. “In dogs suspected of having SAS, the most important test is echocardiography (cardiac ultrasound of the heart and blood vessels) to identify elevated aortic flow velocities and/or subvalvular lesions. Even echocardiography is not perfect as there is a range of aortic flow velocity values that are inconclusive. Some dogs in this range that we termed equivocal for SAS are truly normal dogs while others have very mild disease.

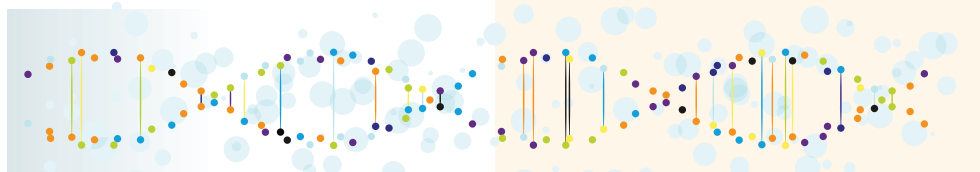
“Echocardiography is the only way to determine if a dog is truly abnormal,” he says. “You cannot overestimate aortic velocity, as a truly abnormal result in a calm dog should be taken seriously. Dogs that are clear for SAS by auscultation (stethoscope examination) alone may not be good enough. Soft murmurs may be difficult to hear in excitable dogs. Furthermore, excitement alone can generate heart murmurs that are indistinguishable from SAS, a common finding in many breeds that suffer from SAS such as Golden Retrievers and Rottweilers.”

Although rare, SAS can occur in children. Their treatment may involve surgical removal of the ridge or ring below the aortic valve. In dogs, such a surgical procedure has not increased survival, plus few veterinary hospitals offer open heart surgery for dogs. Medical management with beta blockers may help delay the onset of more severe disease, such as sudden death and congestive heart failure, in dogs with SAS.

The Future of SAS Research

Understanding the genetics that cause SAS may one day lead to a direct DNA test to help Rottweiler breeders reduce disease incidence. It also may lead to new drug therapies to target affected genes.

“If we knew that upregulating or downregulating a gene with a mutation would help dogs with SAS, that would be brilliant,” Dr. Stern says. “Pharmacogenetics, the study of how genetic differences can affect individual responses to drug therapies, offer hope as well. I’d love to be able to know from the outset



PICALM Gene Mutation Linked to SAS in Newfoundlands

Ten years after research began, a [gene mutation for subvalvular aortic stenosis \(SAS\) in Newfoundlands was discovered](#). The welcome news came none too soon, as Newfoundlands are the most overrepresented breed affected by the potentially fatal heart disease.

The slow process of discovery involved a committed effort by the Newfoundland Club of America and researchers. The research is still ongoing as the team continues to search for modifying genes and other possible causative mutations.

Veterinary cardiologist Dr. Joshua Stern of the University of California-Davis led the research that identified a causative gene mutation. A three-nucleotide exonic insertion in the phosphatidylinositol-binding clathrin assembly protein (PICALM) was associated with the development of SAS in U.S. Newfoundlands. A whole genome analysis screening thousands of genes from 93 Newfoundlands and 180 control dogs of 30 breeds led to the discovery in 2013.

A pedigree analysis of a family of 45 Newfoundlands supported an autosomal dominant pattern of inheritance. This means that only one parent must carry the PICALM gene mutation for offspring to inherit the disease, and not all dogs carrying the mutation will develop SAS. A direct DNA test is now available to help breeders identify Newfoundlands that carry the SAS gene mutation.

“Now that we know one gene that is responsible for SAS and more about which proteins are involved, we can move forward to consider novel therapies that may help treat this devastating condition,” Dr. Stern says. “Finding the mutation is great, but understanding how it does what it does is really important because eventually we’d like to develop novel treatment options for dogs that are severely affected. We continue our work in Newfoundland SAS as this is a complex disease and it appears that there is at least one other gene responsible for this disease in the breed.”

which drugs are going to work. Genetics can help us do that. I think it is a wave of the future.”

Breeders face tough decisions in choosing which dogs to breed. Trying to perpetuate the best qualities of their dogs while avoiding producing puppies with SAS and those that carry the SAS gene or genes can be challenging.

As Rubens says, “It is my dream that we will eventually know how this is inherited and have a test to identify SAS and control this terrible disease in Rottweilers. I believe that research will turn these results.” ♦

Purina thanks Liz Wertz, past president of the Rottweiler Health Foundation, for helping us to identify this topic for the *Rottweiler Update*.

PPCP Raises More Than \$3 Million for Canine Health Research

Since it began in 2002, the Purina Parent Club Partnership (PPCP) Program has raised more than \$3.07 million to support canine health research funded by the AKC Canine Health Foundation. Rottweiler enthusiasts who are members of *Purina Pro Club* and who have designated Rottweiler as their breed of dog and submitted [weight circles](#) from qualifying *Purina* brand dog foods have contributed to the \$69,173 given directly to the American Rottweiler Club through PPCP since 2002. An annual donation based on the value of the submitted weight circles is split between the parent club's Donor Advised Fund at the Foundation for canine health research and the parent club for education, research and rescue efforts.

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Ann Viklund of Purina, center, presents the 2015 PPCP donation to Dr. Diane Brown, CEO, and Dr. Duane Butherus, chair, of the AKC Canine Health Foundation.



'Rumor' Wins 2015 Purina Pro Plan Champions Cup

The No. 1 all-breed show dog in the country in 2015, the German Shepherd Dog "Rumor," also tallied the most points to win the *Purina Pro Plan* Champions Cup. Among her prizes, Multi-BIS/Multi-BISS GCH Lockenhaus' Rumor Has It V Kenlyn received \$10,000 and an original oil painting by accomplished canine artist Linda Draper. The 4-year-old female, who was handled by breeder-owner Kent Boyles of Edgerton, Wisconsin, won 175 Bests of Breed, 154 Herding Group Firsts, 93 Bests in Show, and 33 Reserve Bests in Show in 2015.

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GCH Lockenhaus' Rumor Has It V Kenlyn, the No. 1 all-breed show dog in 2015, wins the *Purina Pro Plan* Champions Cup.

Purina Pro Plan Introduces BRIGHT MIND for Adult Dogs

Purina Pro Plan recently launched *BRIGHT MIND* Adult Formulas to help support the cognitive health of adult dogs. The breakthrough nutrition includes a blend of brain-supporting nutrients, DHA and EPA, B vitamins, antioxidants, and arginine to help support a dog's cognition throughout adulthood. *Purina Pro Plan BRIGHT MIND* Adult Chicken & Rice Formula and Adult Small Breed Formula have optimal levels of high-quality protein, including chicken as the first ingredient, and fat to help maintain ideal body condition. These dog foods also have vitamin A and linoleic acid, an omega-6 fatty acid, for healthy skin and coat, and EPA, an omega-3 fatty acid, and glucosamine for joint health and mobility.

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Want to Reach the Editor?

Have comments about the *Rottweiler Update*? Send them to: Barbara Fawver, Editor, Nestlé Purina PetCare, 2T Checkerboard Square, St. Louis, MO 63164 or via email at editor@purina.nestle.com.

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