



## Q+A with Josh Stern

At just 32 years old, Dr. Josh Stern, DVM, the chief of the UC Davis Veterinary Medical Teaching Hospital's cardiology service and director of the cardiology residency program, already has the resume of a man twice his age. The author or co-author of more than 40 publications and abstracts, his award-winning investigations into the causes of inherited heart disease in animals have garnered him numerous veterinary grants—and led to major breakthroughs in disease identification and treatment. Most recently, he successfully identified a mutation responsible for the development of subvalvular aortic stenosis (SAS) in Newfoundland dogs, as well as a mutation responsible for sudden death and long QT syndrome in a family of English springer spaniels. CCAH funding has helped support all of his current research. In this interview, Dr. Stern talks about his recent discoveries, his motivation, and his vision for the kinds of cardiology breakthroughs he hopes to achieve at Davis in the near future.

**Q:** How did you get interested in veterinary cardiology?

**A:** It started even before I went to vet school. As an undergraduate at Ohio State, I studied sled dogs, which sparked an interest in cardiovascular physiology. That curiosity—along with an equally strong interest in genetics—developed even further during vet school.

**Q:** What made you come to UC Davis?

**A:** It was the right place, right time effect. Dr. Mark Kittleson—a really great cardiologist here—had just retired, and they were looking for a faculty member. The draw of UC Davis's world-class cardiology service plus the genetics research division within the CCAH made it the perfect place for me. I love that part of my job is to help train residents who are just as interested in cardiology research as I am.

**Q:** There are so many heart conditions you could study. Why inherited heart disease?

**A:** My combined interest in genetics and cardiology makes inherited heart disease a natural path for me—and I think it's also one of the most important disease types to study. Not just because of the significant effect they have in dogs and other animals but because I also have a strong interest in comparative medicine, and a lot of these disease processes are shared between animals and people.

**Q:** What is subvalvular aortic stenosis (SAS)?

**A:** It's an abnormal ring or ridge of tissue below the aortic valve in the heart that makes it difficult for blood to be pumped out of the heart and around the body. When it's severe, it's a really bad disease to have. Dogs that are severe and not treated have an average survival time of 19 months. But dogs that are mildly affected are the opposite. They can live a completely normal lifespan and quality. So it's an interesting disease because of the wild variation. The

ability for mildly affected dogs to live a normal life means that many of them are never identified and never see a veterinarian for their heart, and unfortunately they get bred and propagate this lesion within the population. I really want to try to eradicate this disease from breeding lines.

**Q:** How prevalent is the disease among dogs? Does it mostly affect Newfoundland dogs, the breed that you've studied?

**A:** Newfoundland dogs are the most overrepresented breed that we see, but SAS is the most common congenital heart defect in dogs, period. There are no good studies that look at the absolute incidence of it in the population, but it is very, very common.

**Q:** If you have a Newfoundland dog, is it something you know to look out for?

**A:** If you're a Newfoundland breeder, absolutely. Newfoundland dog owners may or may not know about it. But if you Googled Newfoundlands and diseases, it would probably be one of the top search returns.

**Q:** Is all SAS inherited?

**A:** It doesn't have to be, I suppose. But the SAS dogs that we recognize do have a familial or inherited component. Newfoundlands are just the most prevalent one. Golden retrievers and Rottweilers get it really commonly as well.

**Q:** How did your study of SAS come about?

**A:** I started evaluating Newfoundlands when I was a vet student at Ohio State. I collected a lot of DNA samples, looking at Newfoundland pedigrees and trying to piece together how this disease was inherited. As I moved on in my career and studies, I became interested in looking at them genetically to see if we could identify a mutation responsible for the disease. And so we did that, and that's how we identified the mutation, which is in a gene called PICALM.

**Q:** Was the PICALM mutation hard to find?

**A:** I've been at it for 10 years. So it hasn't been so easy going.

**Q:** What was that moment of discover like?

**A:** It wasn't very earth-shattering when it happened, because when you get genetic data back you just start chipping away at all the changes that were found. We received new data where we looked at the entire genome of affected Newfoundlands, and eventually we came across PICALM and it looked to be interesting. Then we had to screen hundreds of normal dogs for the mutation to make sure it matched up with affected Newfoundlands. So even after the discovery day, it took more than a year to confirm that this was really what it was. And then after that we dove into trying to figure out how the mutation happens. To do that, we started looking at development in the gene in other species—specifically, frogs. Finding the mutation is great, but understanding how it does what it does is really the important part for us, because eventually we'd like to develop novel treatment options for those dogs that are severely affected.

**Q:** What does the identification of the PICALM mutation mean for breeders?

**A:** Newfoundland breeders have been incredibly supportive of our research all along, and they were among the first people we told about this discovery. We also developed a DNA-based test that they can use to screen their dogs for the mutation and make responsible breeding decisions

about reducing the prevalence of this terrible disease. Our genetics lab just started offering that mutation test to breeders.

**Q:** You mentioned that the disease is also prevalent in golden retrievers and Rottweilers. Could this test be used for them as well?

**A:** Actually, golden retrievers and Rottweilers do not commonly have the same mutation. They have something else, and we're looking feverishly for what it might be. Right now, I'm looking at SAS in about six other breeds, hoping that we can find the mutations that cause it in these other breed pools. The CCAH is providing seed funding for that work.

**Q:** SAS also affects human children. Are there any implications of the finding of the PICALM mutation for the study and treatment of the disease in people?

**A:** I'm not sure yet. But certainly the knowledge that this gene interacts in the development of the heart is really important for researchers in human medicine. I would foresee that researchers who are studying SAS in humans might specifically look at PICALM in the future.

**Q:** You've also found a mutation involved in long QT syndrome and sudden death in springer spaniels. Is that related to SAS?

**A:** It's different, but it's another inherited disease. Finding the inherited causes of sudden death in animals is a really big thing. We're looking at this in race horses and also in dogs right now. We're also doing a lot of research on inherited heart muscle disease in cats, particularly a condition called hypertrophic cardiomyopathy. Hypertrophic cardiomyopathy is a big problem in humans, causing sudden death in young adults. I hope to help both cats and people by trying to figure out this condition.

**Q:** What other big research goals are looming for you?

**A:** I would love to get to the point where we understand the genetic basis of inherited heart disorders like SAS well enough that we can start developing drug therapies that target the affected genes. If we knew that up-regulating or down-regulating a gene that we found a mutation in would help dogs with SAS, that would be brilliant. And so that's a big aim of our studies. I'm also trying to develop a program here on pharmacogenetics, which is the study of the ways that genetic differences can affect individual responses to drug therapies. It's becoming a big area of study in humans, and I'd like to see that be the case for animals as well. What if we could identify some mutation in dogs that we believe impacts the way that they'll respond to heart medication? As a veterinarian, I'd love to be able to know from the outset which drugs are going to work, and genetics can help us do that. I think it's a wave of the future.