



The following Q & A with Dr Noa Safra addresses spinal dysraphism, (sometimes called “hoppers”) a neural tube defect that affects Weimaraners.

The Veterinary Genetic Lab at UC Davis is currently in the process of developing an affordable, reliable DNA test for spinal dysraphism in Weimaraners. When available, this test may be performed on samples previously evaluated for hypomyelination and hypouricosuria, (for the same Weimaraner) at a discounted price.

Q+A with Noa Safra

Dr. Noa Safra, PhD, DVM, is a post-doctoral fellow in the Bannasch Laboratory at UC Davis School of Veterinary Medicine, where she studies canine hereditary diseases. She is also a long-time owner and breeder of Weimaraners—and it’s her love of the breed that made her determined to find the gene involved in spinal dysraphism—a neural tube defect that affects about 1.4 percent of Weimaraners. Here, she talks about the origins of the CCAH-funded study, its findings, and its considerable implications for human medicine.

Q: How did you decide to do this study?

A: It’s very personal. Fifteen years ago, when I was a vet student, I had my first litter of Weimaraner puppies. Three out of ten had spinal dysraphism. When I went to the library to read more about it, I discovered that the disorder was very well documented. However, on the molecular level, the exact gene

and mutation were never mentioned, and nobody was looking into it. The technology and tools to perform genetic studies weren’t very advanced back then—but now they are. So I decided to see if I could find the genetic mutation that causes the disease.

Q: How prevalent is spinal dysraphism in Weimaraners?

A: It was more prevalent many years ago, but now it is less common. We estimate it to be about 1.4 percent within the breed.

Q: Are other dog breeds affected?

A: A number of breeds, even mixed breeds, can be affected by neural tube defects. All of these defects present differently, because it depends where along the spinal cord the defect is. But this specific defect—spinal dysraphism, caused by the gene mutation we found—is unique to Weimaraners. It mostly affects the end of the spinal cord, near the tail or the lumbar area.

Q: What are the clinical signs of spinal dysraphism?

A: When dogs with the defect are born, they are unable to move their rear legs in normal fashion. They can’t walk or run like other puppies and drag themselves using their front end. When they get stronger, they start moving their back legs simultaneously, giving the appearance of “bunny hopping.” They might also have other neurological symptoms such as ataxia, which affects their coordination. However, spinal dysraphism is a non-progressive disorder, meaning

that while it doesn't get better it doesn't get worse, either. Even the most severely affected puppies make perfect pets. They move and they play and they're happy, and they don't suffer pain. So it's mostly just a very large deviation from normal dog movement.

Q: What happened to the three affected Weimaraners in your litter?

A: They were born in 1998, so they are no longer with us. But they all found great homes. Interestingly, DNA from one of these dogs became part of our study and helped us find the mutation. The puppy's name was Monica. Eventually, I collected enough DNA samples from affected Weimaraners to run a genome wide association study and apply for funding from CCAH. But those first puppies definitely changed my career goals. My mind was really set to go out and study Weimaraner inherited disorders.

Q: And what did you find?

A: We compared the DNA sequences of four affected dogs to the sequences of 96 unaffected dogs. The question you ask in this kind of study design is: where and how are these sequences different? In doing that, we were quickly able to zoom in on one region of one chromosome that had a limited number of genes. We were mostly interested in one candidate gene in that region. We also had evidence from studies in mice that when this particular gene is disrupted, the mice showed movement that was really similar to the Weimaraners—they hopped with their back legs. When we sequenced the coding area of this gene, we found a change in the DNA. We were pretty convinced that we had found the cause of the disease.

Q: Now that you've found the mutation, what happens next?

A: Our next step is to develop a reliable, affordable DNA test for the mutation and then offer it to dog owners, veterinarians, and dog breeders to help them select against the defect. In Weimaraners, with just a 1.4 percent carrier frequency, there is no reason not to eliminate the problem completely. The DNA test could also help a veterinarian who isn't sure what he's looking at reach a diagnosis. In some cases—maybe it's a rescue dog, or a dog whose background and history are unknown—the presentation of the defect could be identical to the presentation of a dog who was hit by a car a long time ago and healed. It would help for the new owner to know that the problem is not progressive—it's not going to get worse. Of course, I still believe that Weimaraners are great dogs with or without the defect. I've had Weimaraner breeders contact me saying they had puppies with the defect and their veterinarians wanted to put them down. And I was able to happily inform them that that wasn't necessary.

Q: Your findings also have implications for human medicine. How so?

A: We know that dogs are really good biomedical models for humans. For the most part dogs have a much simpler genetic makeup than people; human genetics—and neural tube defects in humans—are both much more complex. So any discovery that might lead to treatment or prevention of these defects is really, really meaningful in human studies. Discovering this gene in dogs presents human researchers with a huge opportunity to test humans for mutations within the same gene.

A few of the authors on our study are pediatricians from the University of Iowa. We told them about our finding and that we had great certainty that the mutation led to neural tube defects in dogs, and suggested they might look at this same gene in their human patients. They started looking into the gene and screening more people to see how common it was to have mutations in this gene, and now they are writing grants to continue this study. So for human medicine, it's exciting because this is a great opportunity to learn more about the genetic component of neural tube defects—and it's really only possible because of these dogs. Not only have they helped find the cause of a disease that we can now help eradicate, but they're helping direct pediatricians to a new pathway, new prevention or treatment, or just more understanding of this kind of disease.

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