Nena Winand, DVM, PhD (now retired), was a Senior Research Associate at the College of Veterinary Medicine, Cornell University, Ithaca, NY, and was interviewed by Thomas Reed, Ph.D., MPH, the Breeding Director of the Warmblood Studbook of Ireland.

It looks like WFFS1 suddenly burst on the scene in the last couple of months. But it is not a new syndrome. Please give us a brief history of WFFS1 and your role in its discovery?

A WFFS1 is certainly not a new disorder. The mutation that causes this disorder may trace back to the mid-1800’s or earlier, based on inferences from the pedigrees of carrier affected horses that I studied while a faculty member at Cornell University College of Veterinary Medicine. I became aware of the syndrome when Dr. John Baird (the University of Guelph veterinarian who developed the DNA test for JEB in Belgian horses) contacted me about a foal that had been presented for necropsy to a Canadian lab in the early 1980’s. The pathologist who worked up this case did an excellent job. She and Dr. Baird both felt strongly that the foal had a collagen-related defect, an Ehlers-Danlos type of presentation. The Ehlers-Danlos syndromes (EDS) are a group of connective tissue disorders that are inherited and vary in how they affect the body and in their genetic causes. They are generally characterized by hyperextensibility of joints and hyperextensibility and/or fragility of skin and other collagen-rich tissues. They contacted me because I had been working on HERDA (which is one type of EDS in the horse). This was many years ago; fairly early in my work on HERDA. The foal was from a prominent breeding facility, and they were concerned about the possibility of this condition being inherited. No biological samples were available from that affected foal that would have been useful for genetic or biochemical studies. The breeders, however, were glad to provide blood samples from the sire and the dam of that foal, and from some of their unrelated warmbloods. I processed the blood samples for DNA isolation, but this project had to wait on hold for years, because just having DNA from these blood samples did not really give me an avenue to study anything in an efficient manner. Several years later, after the cause of HERDA had been identified, a veterinarian from the Wisconsin Equine Clinic contacted Dr. William Miller (a well-known veterinary dermatologist at Cornell) and me about a foal that was born with what is now recognized as WFFS1. It was an extremely severe presentation with striking resemblance to the cases I had seen in the Canadian foal, and this foal also was euthanized. The mare owner was devastated and wanted to know what was wrong with the foal. That clinic was able to do a very good workup on the foal, with a lot of photographs and pathology work, and saved tissues that could later be used for biochemistry and genetic studies. I received those samples and immediately processed them to isolate DNA and to sequence the gene encoding lysyl hydroxylase 1. This one was easy to do; we had all the sequence available due to how we approached the issue of HERDA. Within 24 hours I had identified a homozygous mutation in that gene, which was easily predicted (knowing the protein structure of lysyl hydroxylase) to be devastative. I had a blood sample from the dam to check. The stallion owners refused to cooperate, so I could not obtain a sample from the sire. The dam was heterozygous for that mutation (meaning she was a carrier), which is consistent with a recessive phenotype where the mutation has to be inherited from both parents. We knew from human EDS VI studies, where mutations in the same gene are seen, that half of the lysyl hydroxylase I enzyme is usually enough to give a normal phenotype in carriers and the inheritance pattern is recessive. I had a lot more information from the Canadian breeders of the earlier affected foal with extensive pedigrees that accompanied the blood samples of related and unrelated horses. I went back to the samples from the parents of that foal and other warmblood horses provided by that breeder (since I did not have the affected foal) and blind-tested them, demonstrating that both the sire and dam of that foal were carriers of the same mutation. We followed up with a small population survey that demonstrated an approximate carrier frequency of 10% - 15% in 1000-old DNA samples from local warmblood studbooks from various studbooks. In collaboration with Dr. Hans Peter Böckinger at Strohmers Children’s Hospital in Portland, with whom I had worked quite a bit on HERDA, cyclophilin B, and kryls lysyl hydroxylase function, we performed protein function studies. We recognized that the mutation causing WFFS1 previously had been extensively studied at the genetic and biochemical level in a human family. Subsequently Cornell University Read an international patent application for the WFFS1 DNA test, and tests for the mutation can be performed in laboratories throughout the world.

What are the best practices studs owners and stallion owners should follow?

A Test your mares and stallions to identify carriers and avoid breeding carrier mares to carrier stallions. This means asking the stallion owner or the studbook the status of the stallion you are considering for your breeding program. If a stallion owner is not transparent about the carrier status of the stallion, then you should really be a red flag indicating you may want to do business elsewhere. I also advise testing any horses at risk for HERDA before breeding to warmbloods (and testing these for WFFS1), and not crossing carriers of these two disorders. It is crossing a mare that tested positive for the WFFS1 or the HERDA mutated gene with a stallion that tested positive for the WFFS1 or the HERDA mutated gene. And avoid warmblood stallions that have not been tested for WFFS1, regardless of breed or registry. Some are calling for departments of agriculture to require the culling of carrier stallions. What is your view on this?

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A I am not an advocate for immediately culling carriers of this trait (or any isolated autosomal recessive trait that emerges in performance animals). I believe that breeding programs around stringent selection against a single genetic defect could alter the level of performance that we see in these elite bred athletes and in the populations that adopt a cutting policy. Carrier horses have been excellent performers in both jumping and dressage and have many desirable traits that we should abstain to keep in the gene pool. Perhaps over time outstanding horses that are non-carriers can be sorted out and the carrier frequency can be slowly reduced if necessary, but this type of change is best effected over many generations.

Is there any other important information you would like share?

A A question that has been raised is whether carriers are truly ‘normal’. When we talk about recessive and dominant phenotypes we are usually talking about the whole animal, and WFFS1 carriers do appear clinically normal and some, as I have said, are outstanding athletes. However, the distinction between dominance and necessity is not as clear when we study traits of the tissue/cellular and biochemical level. In the case of connective tissue fragility syndromes such as WFFS1 or perhaps even HERDA we have never had to deal with the bane of an extreme performance related repetitive stress can cause in collagen-rich tissues be important to the health and performance of carriers or non-carriers. This is an interesting and potentially important question for science, breeding, and sport but it is something that has not been systematically studied.

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