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First Molecular Genetic Test for a Common Inherited Disease in Companion Animals

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Small animal practitioners, breeders, and pet owners recognize that inherited disorders occur commonly and are a major problem in companion animals. Over 400 hereditary diseases have now been reported in dogs; many of them are breed-specific and may occur frequently in a particular breed due to inbreeding or linebreeding practices. Most genetic disorders are inherited as autosomal recessive traits, i.e., affected puppies of both genders have two mutant genes and result from matings of healthy parents that each carry a normal and mutant gene (carriers).

Each inherited disorder presents with typical signs early in life, and the disease course is usually chronic, although intermittent and late onset presentations are seen with some defects. Since other diseases may cause similar clinical signs, routine and special laboratory tests are generally required to confirm a clinical diagnosis. For the control and eradication of genetic diseases it is also important not only to recognize affected animals, but also to identify carriers among littermates and other relatives of diseased animals. Parents of affected animals are obligate carriers. Unfortunately, laboratory tests to screen for healthy carriers are only available for a few inherited diseases in companion animals. They are usually cumbersome and technically demanding, and do not always permit a reliable differentiation between carriers and normals.

The first molecular genetic screening test for a common inherited disease in companion animals has been developed by Dr. Urs Giger's laboratory in the Section of Medical Genetics at the School of Veterinary Medicine, University of Pennsylvania. The test identifies carriers and affected dogs with phosphofructokinase (PFK) deficiency.

Less than a decade ago, Dr. Giger, associate professor of medicine and medical genetics, first described PFK deficiency in English springer spaniels. PFK, a major regulatory enzyme in all cells of the body, catalyzes the metabolism of sugar and is pivotal in the production of

energy to maintain normal cell function. Dogs with this enzyme deficiency have diseased red blood cells and muscle cells.

PFK deficiency can present as a mild to life-threatening episodic illness. A hallmark sign of this disease is intermittent dark urine, with the color of the urine ranging from orange to dark coffee-brown, which commonly develops following strenuous exercise, prolonged barking, and extensive panting. These conditions accelerate the destruction of red blood cells in affected dogs, resulting in dark brown urine, and in severe forms, pale gums (anemia) or jaundice (yellow coloration of skin and gums) with fever and poor appetite. Particularly in field trial dogs, clinical signs of weakness, exercise intolerance, poor performance to outright refusal to move, and muscle cramps may be observed. Clinical manifestations usually resolve within hours to days. Affected dogs have a relatively normal life expectancy, however, situations that can precipitate such crises should be avoided.

This disorder is inherited as an autosomal recessive trait and has now been identified in over 50 English springer spaniels. It appears to be more common in the field trial line than in show dogs, but the true frequency of affected and carrier dogs is not known. Furthermore, the same disease has also recently been found in an American cocker spaniel.

Dr. Bruce F. Smith, a graduate student and Kleberg fellow in Medical Genetics at Penn's veterinary school,

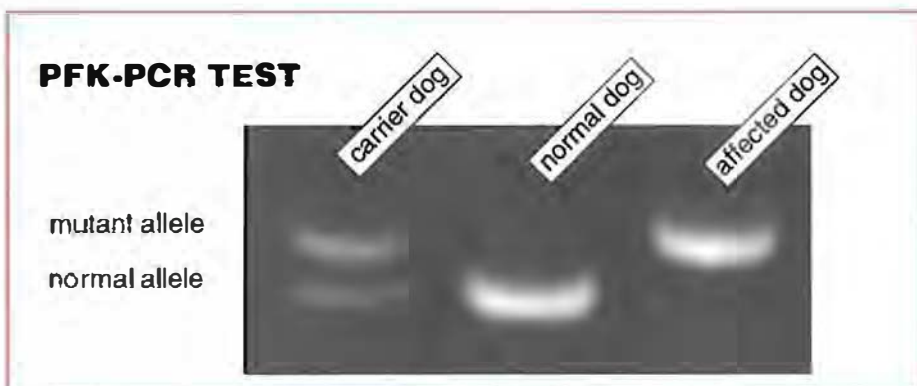


Dr. Smith and Giger with a PFK affected English springer spaniel puppy.

discovered that PFK deficiency and the associated clinical features are caused by a single base pair change (mutation) in the genetic code of the gene for this enzyme. Thus far, only a handful of hereditary diseases in the dog have been characterized at the molecular level, PFK deficiency being the first common hereditary disorder.

Such genetic information is needed to better understand the mechanism of the disease process, and is essential to establish mutation-specific screening tests. The molecular genetic screening test for PFK deficiency developed by the Penn researchers is accurate in determining whether a dog is normal, affected, or a carrier. The test reveals two mutant PFK gene copies in affected dogs, one mutant and one normal PFK gene copy in carriers, and two normal PFK gene copies in normal dogs.

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First molecular genetic test

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The test requires only a few drops of blood from which the genetic code (DNA) is extracted and tested for the presence of the mutation by a polymerase chain reaction, a modern laboratory technique. Dogs can be tested at any age, even right after birth, allowing early determination of whether an animal has affected, carrier, or normal status.

Because of the intermittent and variable clinical signs and the suspected high prevalence of PFK deficiency in the English springer spaniel breed, Dr. Giger

recommends the testing of all English springer spaniels with suggestive clinical signs and all springers used for field trialing or breeding, or prior to purchase of a springer puppy. Affected dogs should not be bred, and appropriate precautions taken to ensure their health and welfare. It is not recommended that carrier dogs be used for breeding; however, if they are bred, they should only be bred to dogs tested as normal, and all of the resulting puppies should be tested. Carrier puppies should be neutered and

normal puppies used to continue the breeding program. By testing and breeding appropriately, PFK deficiency can be rapidly eliminated from this breed, and the further spread of this disease and future suffering of affected animals can be prevented.

For further information on testing dogs, please contact Drs. Urs Giger/Beth Callan, School of Veterinary Medicine, University of Pennsylvania, 3850 Spruce Street, Philadelphia, PA 19104-6010 (FAX 215-573-2162).

National Award for Penn Researcher

A Burroughs Wellcome Fund New Investigator Award in Molecular Parasitology for 1993 was awarded to Dr. Phillip Scott, assistant professor of parasitology at the University of Pennsylvania School of Veterinary Medicine. The \$60,000 award, provided over two years, will enable Dr. Scott to continue his work on the development of a vaccine against leishmaniasis. This disease, caused by a parasite, affects man and animals in Central and South America, Africa, southern Europe and the Middle East. If not treated it can cause severe disfigurement and even death.

Dr. Scott's research focuses on studying the immune responses associated with the parasite, *Leishmania*. The foundation for the studies are Dr. Scott's observations that the stimulation of different types of immune cells determine whether the parasite is eliminated, or whether the infection is eventually fatal. These findings are useful not only in understanding leishmaniasis but also in understanding immunity in several other diseases, since these different cell types are important in controlling many infectious diseases, including parasitic, bacterial and viral infections, as well as allergies and autoimmune disease. Thus advances made in the leishmanial model may be widely applicable.

In the past, vaccine development has been, for the most part, done empirically. Dr. Scott's research will involve



identification of molecules that act to stimulate the development of particular types of immune cells. With this knowledge, it is thought that researchers may be able to design vaccines of the future more rationally.

The Molecular Parasitology Award Program is offered annually by The Burroughs Wellcome Fund to recognize the pioneering contributions of Sir Henry Wellcome to the study of tropical medicine, and to support the application of modern developments in biology and

chemistry to the understanding, control and prevention of parasitic diseases.

Dr. Scott is the first researcher associated with a veterinary school to receive the award. Two other 1993 New Investigator awards were presented to scientists at other institutions.

The Burroughs Wellcome Fund is a private, non-profit foundation established in 1955 "To provide financial aid for the advancement of medical knowledge by research, and for other scientific, scholarly and educational purposes."