JUVENILE RENAL DYSPLASIA (JRD) DNA TESTING

Discovery of the Mutation and development of a direct DNA test for JRD.

Background
Juvenile renal dysplasia (JRD) is an important category of kidney diseases in canines. Dysplasia is defined as abnormal growth or development of cells or organs. In the case of JRD the kidney fails to develop properly during embryogenesis in the womb. At birth immature structures consisting of undifferentiated fetal cells or tissue types are found in the kidney, and are persistent throughout the life of the animal.

Many breeds of dogs are afflicted with JRD, and this has been documented in veterinary text books, as well as case reports and articles in the scientific literature. Of note is that JRD in these breeds share a common phenotype, characterized by immature glomeruli, and/or tubules and persistent mesenchyme.

The mode of inheritance of JRD has been widely debated, as this disease can present itself with a wide range of symptoms and pathological findings. Definitive diagnosis of JRD is done by a wedge biopsy which reveals dysplastic lesions, including abnormal ducts, and glomeruli. Individuals with an abnormal biopsy can be asymptomatic, showing no signs of the disease, On the other hand, they may present with classic signs of chronic end stage renal failure, or somewhere between these two extremes. Given this broad spectrum of symptoms affected individuals often go unnoticed, and remain in the breeding population. This is why development of a genetic test is critical to the management and elimination of this disease. Further a genetic test will shed light on the mode inheritance.

The gene for JRD is discovered and a direct genetic test is developed.

During the development of the fetus, certain genes act in a pathway or cascade to direct the development of the various organs and structures that make up the body (think of it as dominos: if one domino is missing the other ones won't perform their task in the array). Since every cell contains two copies of every gene, one non-mutated copy may be sufficient to complete to cascade (recessive inheritance). The human genome contains about 20,000 to 25,000 genes, and the canine genome is likely to contain about the same number. Of these several hundred or more may be dedicated to the maturation of specific organs. Not all of these "tissue specific" genes are absolutely essential to the development of specific cell types, as has been shown in "knockout mice", where genes have been completely eliminated with no observable effect on the animal. In the case of renal dysplasia in model organisms such as the mouse, mutated transcription factors (genes that code for proteins that turn on other genes) or growth factors (genes that code for proteins that promote the growth of cells), have been implicated in causing the disease.

One approach to discover genes that are cause genetic diseases is to use candidate genes known to cause specific diseases in model organisms, like the mouse, rats, zebra fish or even the lowly fruit fly.

This was the approach used in the quest to find the mutation for JRD in dogs. After DNA sequencing six candidate genes, the causative mutation was finally uncovered in a gene in Lhasa apsos, and Shih Tzus. This mutation was then discovered in other breeds with JRD, and a direct genetic test is now available for many breeds afflicted with this disorder.

Through pedigree studies, the mode of inheritance was finally revealed as Dominant with Incomplete Penetrance.

What does Dominant with Incomplete Penetrance Mean?

All chromosomes exist in pairs in the nucleus of cells. Each pair is comprised of one chromosome from the sire and one from the dam. Therefore, every animal has two copies of every gene. In dogs there are 78 chromosomes, or 39 pairs.

The traits that we see in an individual are collectively known as the "phenotype", while the "genotype" refers to genetic constitution or makeup of an individual.

A mutation is a permanent change in the DNA sequence of a gene, whether it is good, bad or neutral. Mutations that cause a genetic disease can be inherited as dominant where one bad copy of the gene is sufficient to cause disease or a phenotypic trait to be observed, or recessive where two bad or mutated copies of the gene are needed to cause disease or phenotypic trait to be observed.

Dominant with incomplete penetrance refers to a situation where an inherited mutation may or may not be expressed in an individual.

Penetrance refers to the frequency that the phenotype (or some characteristics of the disease) is observed. If for example, the penetrance is 75%, then the chances of offspring to develop a disease are 3 out of 4. In the case of JRD, the penetrance is low, with a penetrance estimated to be about 5%. Therefore only a small number of individuals with the mutation will show signs of the disease. However, they can pass the disease on to their offspring. This is why a genetic test is critical to manage JRD; this is the only way to eliminate this disorder. There may be risk factors or triggers that are yet undiscovered that may increase the chances of an individual to develop JRD.

How can the new test be used to eliminate this disorder from a breed without compromising the gene pool?

Genetic tests are designed to manage and eventually eliminate disorders without compromising the diversity in a gene pool. If you have just found out that your dog carries the mutation for juvenile renal dysplasia, do not panic. Now you have the opportunity to manage and eliminate this disease. The frequency of this mutation is extremely high in many breeds. This mutation has been elusive and impossible to eliminate prior to the development of a genetic test, as the disease appears sporadically because it is inherited with incomplete penetrance.
Meaning that an animal that carries this mutation may or may not show clinical signs of the disease, but can still pass it on to the next generation.

All dogs (and living organisms) are carriers of multiple mutations.

If a genetic disease is produced in an animal, it is not necessarily the result of poor breeding practices, but is the nature of inheritance as a random event. Although the exact mutation rate for caninies is difficult to determine, by extrapolation from other species, there is a good chance that every individual produced has a new mutation in some gene. Therefore, with every generation of breeding, new mutations arise, but since they are present at a low frequency, they are generally lost in subsequent breeding. There is no such thing as a perfect animal!

Chromosomes exist in cells in pairs, one from the sire and one from the dam. Dogs have 39 sets of chromosomes. Each set or pair is composed of two chromosomes, one from the sire, and one from the dam. In the case of a simple recessive mutation, one of the chromosomes, either from the sire or the dam, makes enough protein from for the animal to survive. Therefore, the "wild type" chromosome of the pair provides enough protein (gene product) to compensate for the chromosome that carries a mutation. In the case of a dominant mutation, only one copy of the chromosome carrying the mutation is necessary to produce disease.

With the identification of one of the many mutations that your animal carries, you can now proceed to at least eliminate this identified mutation, and not inadvertently select for another deleterious mutation that your animal carries. **Wholesale elimination of carriers is the worst decision that you can make as this would deplete the gene pool.**

As in any breeding you must consider the positive and negative traits of each partner, and how the parent's traits can best balance and compliment each other.

A brief History of JRD

Throughout the course of my work with the various breeds, breeders who denied ever having a case in their kennel were surprised to find that the mutation was present, or suddenly after years of breeding a litter is born with this disease. This disease appears to be sporadic in nature, and is probably influenced by genetic background.

To those who deny that this mutation is in their lines, I always ask "have you looked, and how many biopsies have you done on your dogs. " The answer in generally that they have not been at all vigilant about this disease in their lines, and when an entire litter goes down at an early age, breeders, except in the breeds that are well known to have this disorder, may not consider the possibility. Many veterinarians have likewise pigeonholed this disease as one of Lhasa apsos, and Shih tzus.

Here is an excerpt form an article written by **Dr. Kenneth Bovee** regarding JRD in Shih Tzus:

"*The prevalence of renal dysplasia in this breed is very high in North America. In a study of 74 random dogs evaluated with wedge renal biopsy, only 16%*

were free of any histologic evidence of the disease. Among the remaining, about 52% had 1-5% fetal glomeruli, while 20% were moderately affected with 6-15% fetal glomeruli. The remaining 12% had more than 15% fetal glomeruli. These findings suggest that the genetic character of the disease is very high and variable in this breed. ***Because many dogs are mildly affected and escape detection in the absence of renal biopsy, the question arises as to the genetic transmission of the defect in normal appearing dogs****."*

In the case of JRD in your breed, ideally animals identified as **carriers** of this mutation should be bred to a clear. In this case, approximately 50% of the offpsring will be clear of the mutation. Breeding individuals with two copies of the gene (homozygous mutant allele = homozygote) to a clear will produce all carriers. This is the only way to eventually eliminate the mutation in these circumstances, but such a breeding is only recommended if this is the only breeding option. And the carriers can then be bred to a clear, in subsequent generations. Obviously and where possible, it is ideal to breed clear to clear. However it is important for your breed to maintain genetic diversity. If the frequency of the mutation in a breed is high, breeders have using carriers and homozygotes in their breeding program all along without even knowing it.

What will happen to the resultant litter if breeders mate 2 of the (c) 'clear' animals together? Dr. Bovee states in his article this mating still produced carrier's 1-3% fetal glomeruli.

Dr. Bovee is referring to two animals that are clear by biopsy (phenotype), not by DNA test (genotype). Animals that have the mutation may have a completely normal biopsy. This is why people who have tried to eliminate this disorder by biopsy (phenotype) have failed. **Only a genetic test can tell you what you are dealing with.**

What does this DNA test actually tell the breeder?

The DNA test results are reported as follows:

a) Carrier (one copy of the JRD mutation)

b) Homozygous mutant allele = Homozygote (two copies of the JRD mutation)

c) Clear.

With a & b results above – the animal is also potentially affected by JRD.

This DNA test information is clearly important for breeders, and important for the future of the breed.

Before the development of this DNA test, JRD could only be positively diagnosed by a biopsy. A biopsy will reveal the phenotype. A wedge biopsy may reveal dysplastic lesions, including abnormal ducts, and immature glomeruli. Individuals with an abnormal biopsy can be asymptomatic, showing no signs of the disease, On the other hand, they may present with classic signs of chronic end stage renal failure or somewhere between these two extremes. Given this broad spectrum of symptoms affected individuals often

go unnoticed, and remain in the breeding population.

Organizations representing breeds that are in need of a JRD test should contact me at Dogenes Inc. **http://www.dogenes.com** to discuss a JRD DNA Test Study for their breed or e-mail me at **info@dogenes.com**

DOGenes uses cheek swabs for DNA testing.
We ask for **three samples per dog**. We also require certain documentation to be completed for test development and **3 to 5** generation pedigree information, if available.

For Further information on testing please visit us on the WEB at
http://www.dogenes.com

Use Your Knowledge Wisely
Protect Your Gene Pool and Preserve Genetic Diversity in your breed

Mary H. Whiteley, Ph.D.
DOGenes Inc.