Papillon Club of America
Health & Genetics

EPIDEMIOLOGICAL STUDIES OF INHERITED DISORDERS

By : Jerold S. Bell
Tufts University School of Veterinary Medicine

Knowledge of the pedigree spread of defective genes allows researchers to determine the population at risk for genetic counseling. With the exportation of animals, and semen, we need a global view of genetic epidemiology. Most breed clubs can provide researchers with computerized pedigree databases for population genetic studies.

When building a pedigree map for a recessive disorder, there is a tendency to trace carrier individuals back to common ancestors and blame these individuals as carriers or progenitors of the defective gene. This is also known as a witch-hunt. The closest common ancestor in an autosomal recessive disorder is the ancestor who traces down to all carriers (parents of affected dogs). The closest common ancestor is usually a stud dog who was used frequently. This is because prolific individuals will become the central convergence points for bringing families together in ancestral pedigree analysis.

The closest common ancestor analysis is a tool used to determine the minimum age of a defective gene in the population,and therefore its possible genetic spread. The analysis allows a breed to determine the breadth of the gene pool that is liable for carrying the defective gene. Knowing the minimal age of the gene in the population provides information on how hard it will be to control the gene in the breed pool. If all affected individuals trace back within one to two generations to a common ancestor, then the mutation may be a recent one, and control should be attainable. If the closest common ancestor traces far back in a pedigree, or is an imported or foundation animal for the breed, then the gene is widespread and control will be more difficult.

The closest common ancestor analysis does not identify ancestral carriers of defective genes. Carriers of a defective recessive gene can only be identified if they; a) have produced an affected offspring, b) are an offspring of an affected individual, or c) genetically test as carriers. The addition of newly diagnosed affected dogs to a pedigree can change the dog who is the closest common ancestor, so that the previously identified dog may not even be involved in the line of descent. The poster will show why you cannot predict that the closest common ancestor is a carrier.

Researchers are tempted to use the Hardy-Weinberg law to calculate a carrier frequency in the population based on the observed frequency of affected individuals. It must be understood that the law is only valid if based on a population in Hardy-Weinberg equilibrium. This requires no selection, and all members of each generation to have an equal chance at reproduction, in equal frequencies. These parameters do not exist in domestic animal breeding scenarios. While it is recognized that the frequency of carriers of recessive defective genes will far exceed that of affected individuals, there is no mathematical relationship between the two in domestic animal breeding. This has been shown in analyzing the results of generations of genetic testing for breed specific disorders. Valid estimates of the frequency of carriers in the population can be determined through population-wide genetic testing or estimated through pedigree analysis.

Pedigree maps of several breed-related autosomal recessive genetic disorders are presented to show differences in the worldwide epidemiology of disseminated, localized, high and low frequency defective genes.

Different forms of cerebellar cortical abiotrophy (CCA) have been researched in several dog breeds. In Gordon Setters, over 60 affected dogs in the United States trace back to dogs imported from England in the early 1940's. Affected dogs have also been confirmed in Holland, and Australia, implicating earlier European ancestors. The defective autosomal recessive gene is an ancient one, occurring at a low frequency. It would not be surprising to diagnose the disorder in any Gordon Setter worldwide.

Hereditary cerebellar cortical and extrapyramidal nuclear abiotrophy in Kerry Blue Terriers was confirmed in several dogs in the United States in the 1970s. Affected dogs traced back to one of two litter brothers within four generations. The national breed club instituted a pedigree publication, test-breeding, and carrier elimination plan, and it was thought that the defective gene was eliminated. Unfortunately, a carrier son of one of the brothers became a prolific sire, with descendents exported around the world. Now, practically all affected dogs trace back to this sire. This is an autosomal recessive gene originally limited in its distribution, but now widely dispersed.

CCA in the Old English Sheepdog has been diagnosed in the United States, Canada, and in England dating back to the late 1970's. Affected American and Canadian dogs descend from different English imports; with common English ancestors of all cases born in the early 1960s. Canadian carriers were exported to Australia, and an import from Australia has now sired affected dogs. This is an example of a recent autosomal recessive mutation that while at low frequency, is spreading around the world.

Scottish Terrier CCA is the highest frequency disorder in the group, with a health survey reported frequency of 0.5%. Affected dogs in the United States, England, Canada, Japan, and South Africa trace back to common English ancestors in the 1960s. This disorder has a broad pedigree background, indicating an old, dispersed gene in the population.

GM_1-gangliosidosis in Portuguese Water Dogs, Labrador Retriever central axonopathy, polioencephalomyelopathy of Australian Cattle Dogs, and Ibizan hound progressive central axonal dystrophy demonstrate additional pedigree
patterns.

BIOGRAPHICAL SKETCH OF : JEROLD S. BELL

DVM is a Clinical Assistant Professor, and Director of the Clinical Veterinary Genetics Course for the Tufts University School of Veterinary Medicine. He was trained in genetics and genetic counseling at Michigan State University, and the University of Missouri. His DVM is from Cornell University. Dr. Bell lectures to all-breed and individual breed dog clubs. He is the project administrator of genetic disease control programs for national parent clubs. He performs genetic counseling through Veterinary Genetic Counseling, and practices small animal medicine at Freshwater Veterinary Hospital in Enfield, CT. He and his wife breed Gordon Setters