DNA TESTING FOR INHERITED DISEASES IN DOGS

The specific reference to Welsh Springers is at the end of the statement.

Inherited diseases are disorders that are passed from one generation to the next. They arise by genetic mutation - damage to a particular gene which can be caused by a number of environmental factors - and will be inherited like any other gene. Recent advances in molecular genetics are now yielding practical results in the identification of disease-causing genes in dogs and a number of DNA-based tests have become available. At the Animal Health Trust, we are offering tests for progressive retinal atrophy (pra) in Irish Setters, for copper toxicosis in Bedlington Terriers and for fucosidosis in English Springer Spaniels.

What are the developments in canine genetics that have made these tests possible? Over the past few years we and others have put together a set of resources to search for mutations underlying canine inherited diseases. A genetic map of DNA markers has recently become available for the dog, providing a framework that we can use to track any inherited trait, including diseases. At the Animal Health Trust, we have pioneered the application of cytogenetic techniques to canine chromosomes; techniques based on visualising DNA probes with fluorescent tags. We are using this approach to identify anchor points for the genetic map and to reveal regions of human chromosomes which match canine chromosomes. The knowledge gained in this way will mean that we will be able to tap into the wealth of information available for human genetics - information that will greatly expand as the Human Genome Sequencing Project reaches completion in the first few years of the next century.

When we begin to study a new disease, we first need to establish the mode of inheritance. Disorders which are inherited in a simple fashion, either recessive or dominant, can now be studied at a molecular level - this includes many forms of PRA and haemophilias. Diseases where more than one gene is involved, such as Hip Dysplasia, cannot at present easily be studied in the general population, although methods to analyse such conditions are under development. Most hereditary disorders in dogs are genetically recessive, that is to say that two copies of the disease-form of the gene, one inherited from each parent, must be present in an individual for that dog to show the disease. Dogs with only one copy will show no symptoms but will pass the disease on to future generations. These asymptomatic carriers are a particular problem since, up until now, there has been no simple way to detect them. DNA testing opens up the possibility of detecting asymptomatic carriers by a simple blood test; carriers can then be excluded from the breeding stock.

Some disorders, such as haemophilia and fucosidosis, have a clearly recognisable human analogue. The mutation can then be located in the canine equivalent of the human gene. Unfortuantely, this is not the case for many, prehaps the majority, of canine disorders. For such conditions we need to narrow our search. We can do this by first locating the region on the canine chromosomes (the microscopic bodies in cells carrying the genes) where the gene for that disorder lies. By comparing the dog's chromosomes with those of humans, we can say which human chromosome corresponds to that canine chromosome and then search databases of genes from that human choromosome for genes likely to be candidates for that disease.

How do we track down the chromosome bearing the disease gene in the dog? By analysing families with the disease, we can identify the DNA marker whose pattern of inheritance most closely

resembles that of the disease. This DNA marker must be near to the disease gene on the chromosome. For these studies, we need to accumulate blood samples, from families with the disease, for around 50 to 60 dogs. We prefer dogs above the age where the disease can be easily recognised and also insist on evidence as to the dog's disease status since the analysis depends absolutely on the diagnosis of the dogs involved being correct. Any wrongly diagnosed dogs can invalidate the study. Once we know the position of the disease gene on the canine chromosomes, we can refer to data on the corresponding human chromosome to identify likely candidate genes. These candidate genes can then be searched for the presence of the mutation causing the disease and a diagnostic test devised. For both PRA in Irish Setters and fucosidosis in English Springer Spaniels, DNA testing is based on a direct test of the disease gene itself. If the specific gene is not known, it is also possible to use DNA Markers close to the disease gene as a diagnostic test, although this will be less useful and will contain a built-in margin of error of perhaps 5% because of the nature of the test. The test for copper toxicosis in use at the moment is of this type.

In collaberation with a veterinary surgeon, Sue Phillips, we have been collecting samples to begin to study epilepsy in Welsh Springer Spaniels. We now have samples from several lines containing individuals affected with epilepsy and will be analysing them making use of the genetic resource that we have available and described above.

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