New DNA test for Late onset ataxia in the Parson Russell terrier

Background

Late onset ataxia (LOA) in the Parson Russell terrier (PRT) is disease of incoordination of gait and lack of balance. The onset age for the disease is usually between 6 months and 1 year of age, when owners may start to notice that their dog is showing changes in gait pattern (often weaving of the hind limbs) and some difficulty balancing. The disease is progressive and affected dogs become increasingly uncoordinated with difficultly balancing, which makes moving around and everyday tasks such as going up and down stairs difficult. There is no treatment or cure for LOA and affected dogs are often euthanized, typically around two years after onset, on humane grounds as their quality of life diminishes.

Genetic investigations

At the Kennel Club Genetics Centre at the Animal Health Trust we have been investigating the genetics of LOA in the PRT. In our initial experiments we performed a genome-wide screen of markers using DNA from 16 LOA affected dogs (cases) and 16 unaffected (control) PRTs. This approach enabled us to locate a small region of the genome (approximately 0.1 %) which was present in 15 of the 16 cases, but not present in any of the controls, and almost certainly contained the mutation causing the majority of LOA cases.

In our second round of experiments we used a technique known as target-enrichment to separate the LOA associated region from the remaining 99.9 % of the genome in 2 cases and 3 controls. The LOA associated region, which still consisted of 2.5 million 'letters' of code, was then sequenced almost entirely using an advanced sequencing technique.

Results in the PRT

Although many sequence variants were identified between the five dogs whose DNA we sequenced, one interesting mutation within the protein coding part of a gene was identified, which is predicted to have a damaging effect. The mutation was investigated in additional cases and controls and found to be very highly associated with LOA in the Parson Russell terrier – in other words, we could use the mutation to predict very accurately whether a dog had LOA or not. Results are summarised in the table below:

	Clinically normal PRT	Clinically affected PRT
0 copies of the mutation	136	3
1 copy of the mutation	68	1
2 copies of the mutation	1	22
Total	**205**	**26**

Out of the 26 LOA affected dogs in our sample collection 22 had two copies of the mutation (85 %). Of the remaining four dogs, three had no copies of the mutation (clear) and one had a single copy of the mutation (carrier). We believe there is a different hereditary (another mutation) or environmental cause (such as head trauma) of ataxia in these four dogs.

We also tested 205 healthy PRTs. 204 of these dogs (over 99 %) were clear or carriers of the mutation. One 4 year old dog that is reported by his owner to be clinically normal has two copies of the mutation, and there are two possible reasons for this:
(a) the mutation that we have identified may work in conjunction with another 'modifier' mutation in the PRT. The modifier mutation would be harmless on its own, but disease-causing when inherited along with the LOA mutation. In this case we would speculate that the modifier mutation is very common in the PRT, and it is therefore rare for dogs to have two copies of the LOA mutation but be free of the modifier mutation and as a result be clinically free from LOA
(b) the mutation that we have identified is not the causal mutation, but is a variant that lies very close to the causal mutation with very high diagnostic value (the LOA mutation correctly predicts the LOA status for 227 of the 232 (97.8%) dogs we genotyped).

Results in the Jack Russell terrier

We have collected DNA from five Jack Russell terriers (JRT) with ataxia. Only one dog had two copies of the mutation, and the remaining four dogs were clear of the associated mutation. The size of the sample collection is too small to draw any firm conclusions, but the results suggest that there may be at least two genetically distinct forms of ataxia in the JRT.

DNA test

Because of the diagnostic value of the identified mutation, a DNA test for LOA in the PRT will be launched on the **1st November 2012** and will be priced **£48**. The test will be based on the LOA associated mutation we have identified and will accurately predict the risk of developing LOA for over 97% of PRTs. Results will be explained as follows:

CLEAR: These dogs have two normal copies of DNA and are highly likely to be clear of LOA. The results of our research suggest that there may be other causes of ataxia in the breed so we cannot exclude the formal possibility that clear dogs could develop a genetically different form of ataxia due to other mutations that are not detected by this test.

CARRIER: These dogs have one copy of the LOA associated mutation and one normal copy of DNA. These dogs will not develop LOA themselves as a result of the LOA mutation but they will pass the mutation on to approximately 50% of their offspring. The results of our research suggest that there may be other causes of ataxia in the breed so we cannot exclude the formal possibility that carriers could develop a genetically different form of ataxia due to other mutations that are not detected by this test.

AFFECTED: These dogs have two copies of the LOA associated mutation and have a very high chance of developing LOA (96 % of dogs studied in our research programme with two copies of the LOA associated mutation were clinically affected with ataxia).

The test will effectively reduce the number of LOA cases in the PRT. We encourage owners to keep us updated on the health of dogs they have tested. We are particularly interested to hear from owners of dogs that:

i) are clinically affected with ataxia but that do not have two copies of the mutation, or

ii) are over 4 years old and remain free from ataxia despite having two copies of the mutation.

This information will help us to monitor the effectiveness of the test, to possibly refine the test in the future if necessary and to start to investigate additional cause(s) of ataxia in PRTs and JRTs.

DNA tests can be ordered online from **November 1st 2012**. Full details available from our website: http://www.aht.org.uk/cms-display/genetics_tests.html

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