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Retinopathy in the Swedish Vallhund is Associated with Dysfunction of the *MERTK* Gene

In the late 1990s veterinarians in Finland and Sweden diagnosed a new type of retinal degeneration in the Swedish Vallhund (SV) breed. Collaborating scientists at Michigan State University and the University of Helsinki clinically examined 324 dogs in seven countries and identified a responsible gene defect (*MERTK*). The identified gene is associated with one of the most common forms of incurable blindness in humans[1,2].

Based on the clinical study the disease can be divided into three different stages. Stage 1, the earliest stage with the mildest clinical signs, was characterized by a diffuse multifocal red or brown discoloration of the retina. The mean age of diagnosis was 4 years, but these abnormalities were noted as early as two months and as late as 18 years of age without any clinical signs of vision loss. In Stage 2, the retina showed signs of degeneration and thinning. The mean age at diagnosis was 6 years. While the majority of dog with these degenerative changes did not appear to have vision problems initially, some owners reported that their dogs exhibited mild to moderate signs of night-blindness as the areas of retinal thinning expanded. Stage 3 is characterized by more diffuse retinal thinning with a mean age of 12 years. These dogs suffered from loss of night-vision and severely impaired day-vision; some dogs were assessed as completely blind.

Genetic research reveals a new gene associated with the disease

The disease has been associated with a *MERTK* gene that is located on canine chromosome 17. An intronic mutation (marker) that is positioned in the non-protein coding region has been associated with the disease. It is not known if the mutation affects the gene function, but it is highly associated with the retinopathy. However, further research is still needed to identify the actual mutation. By studying about 400 dogs the mutation was associated with the disease, if the dog had inherited it from both parents and was homozygous for the mutation. In addition, by studying the gene function in retinal samples, it was shown that the gene was overexpressed in the affected dogs. As the identified marker is significantly associated with the disease, it can serve as a marker to evaluate the dog´s risk for retinopathy.

In SVs the identified marker leads to normal intronic A-nucleotide change to G-nucleotide. Nucleotides form the DNA strand and individual´s genome. Altogether the study included 106 retinopathy-affected dogs. Of these dogs 69.8% were homozygous for the alternate G-nucleotide (GG). 25.5% of the affected dogs had received the A-nucleotide from one parent and the G-nucleotide from the other and were heterozygous (AG). Only 4.7% of the affected dogs were homozygous for the normal A-nucleotide (AA).

In addition to the affected dogs the study included 259 healthy, eye-examined dogs. Of these dogs 24.3% were homozygous for the A-nucleotide (AA). 61.8% were heterozygous (AG) and only 13.8% were homozygous for the G-nucleotide (GG).

Based on these results the homozygous GG-dogs have a **18-fold risk** to be affected with retinopathy compared to a heterozygous AG or homozygous AA dogs. Even though some of the healthy dogs were homozygous for the G-nucleotide (GG), some are still young that they may be affected at older age, as the age of onset is very variable.

The results of the marker test are the following:

AA: The dog has two normal copies of the *MERTK* marker. Only 4.7% of the affected dogs are homozygous AA, so the dog has a minor risk of developing retinopathy. However, other retinal diseases due to some other mutation cannot be excluded.

AG: The dog has one copy of the mutated nucleotide and one normal copy. About 25% of the affected dogs are heterozygous AG and have a minor retinopathy risk. However, other retinal diseases due to some other mutation cannot be excluded.

GG: The dog has two copies of the G-nucleotide. It has been inherited from both parents. The dog has a **18-fold risk** of developing retinopathy. Due to this, the dog should be eye examined regularly to detect the possible degenerative changes as early as possible.

How to use the marker test in breeding

Based on the results a marker test has been developed for the breed to test the dog´s risk for retinopathy. The test is not a gene test because the actual mutation is not known.

However, it should be noted that over 60% of the unaffected dogs were heterozygous (AG) so they carry the risk nucleotide and transfer it to their offspring. This should be taken into consideration when planning breeding strategies. This carrier frequency applies quite well to the whole SV population, as 400 dogs were included in the study. **The carrier dogs should not be excluded from the breeding program** and homozygous GG dogs cannot be avoided with such a high carrier frequency. However, the genetic status estimates the dog´s risk for retinopathy and this should be taken into consideration in the dog´s eye examinations.

Commercial test available spring 2015

To test the dogs in the future a commercial marker test will be available in spring 2015 by Genoscoper co. (http://www.genoscoper.com/en). More information about the time schedule can be obtained by contacting Genoscoper directly.

References:

1. Cooper AE, Ahonen SJ, Rowlan JS, Duncan A, Seppälä EH, Vanhapelto P, Lohi H, Komáromy AM (2014). A Novel Form of Progressive Retinal Atrophy in Swedish Vallhund Dogs. PLoS ONE, PLoS ONE, 9(9): e106610.
2. Ahonen SJ, Arumilli M, Seppälä EH, Hakosalo O, Kaukonen MK, Komáromy AM, Lohi H (2014). Increased Expression of MERTK is Associated with A Unique Form of Canine Retinopathy, PloS ONE.