
New DNA test for craniomandibular osteopathy (CMO) in three Scottish terrier breeds ^b **UNIVERSITÄT BERN** (December 1st, 2012)

Background

Craniomandibular osteopathy (CMO) is a non-neoplastic (not a tumor), proliferative disease altering form and function of the bones of the skull (tympenic bullae) and jaw bone (mandible). This disease is known by several synonyms, such as 'mandibular periostitis', 'Westie jaw', 'Scottie jaw' and 'lion's jaw'. The CMO disease was first recognized in England more than 50 years ago and since that time CMO is suspected to be inherited as monogenic trait. The disease predominates in Cairn terriers, Scottish terriers, and West Highland White terriers and rarely in other breeds of dogs.

The disease is seldom recognized until signs of discomfort during chewing and eating are observed. This usually occurs when the dogs are from 4 to 7 months old. The jaw is bilaterally thickened and several bones become so large and tender that the mouth cannot be fully opened. The tenderness of the affected jaw is associated with intermittent fever of 3 or 4 days duration. This tenderness and fever may recur every 2 to 4 weeks during the bony proliferation phase. Radiography is the best method for diagnosing CMO. Treatment is symptomatic. Most animals can be made comfortable using corticosteroids. However, treatment does not result in cure. Although the primary disease process does not seem to cause death, in some cases euthanasia has been performed because of severe pain and malnutrition resulting from the inability to eat.

Genetic investigations

At the Institute of Genetics, Vetsuisse faculty, University of Bern, Switzerland, and the Department of Veterinary Biosciences and Research Programs Unit, Molecular Medicine, University of Helsinki and Folkhälsan Research Center, Finland, we have investigated the genetics of CMO in Cairn, Scottish, and West Highland White terriers. In our initial experiments we performed a genome-wide association study using DNA from 10 CMO affected dogs (cases) and 41 unaffected (control) dogs of West Highland White terriers. This approach enabled us to map the causative mutation to a small region of the genome on dog chromosome 5. Further experiments revealed that at least one, mostly two copies of the CMO associated chromosome 5 segment was present in all CMO cases of Cairn, Scottish, and West Highland White terriers.

In a second round of experiments we sequenced the whole genome of a CMO affected West Highland White terrier. Our detailed analysis uncovered a single causal DNA mutation for CMO. This mutation alters the coding part of a single gene, and leads to the expression of a defective protein.

The mutation was investigated in a total of 75 cases and 400 controls and found to be very highly associated with CMO in all three affected terrier breeds.

Out of the 75 CMO affected dogs in our sample collection 63 had two copies of the mutation (84%). Of the remaining twelve dogs, ten had a single copy of the mutation (heterozygous), which can be explained with CMO being an incompletely penetrant autosomally dominant inherited disease. Because of incomplete penetrance and varying expressivity, many of the dogs carrying the CMO mutation will live without showing clinical signs. We also tested dogs of all three terrier breeds without reported CMO signs and we observed all three possible genotypes. Within a cohort of 303 West Highland White terriers the frequency of the mutant allele was 36%. These presumed healthy dogs carrying one or two copies of the mutation are used for breeding, whereby the disorder may be perpetuated. We noticed that two CMO diagnosed dogs did not carry the mutation. These dogs possibly represent misdiagnosed cases or are affected due to other unknown genetic or non-genetic causes.

Dogs that are homozygous mutant (two copies of the mutation) have a comparably higher risk to develop CMO. Dogs heterozygous for the mutation (one copy of the mutation) might also develop clinical signs; they are classified at low risk. However, at the moment we don't have a sufficient number of CMO diagnosed dogs to give exact penetrance levels (probability to develop the disease) for the homozygous and heterozygous genotypes, respectively. Furthermore, we have no evidence that the individual severity of the disease is related to the genotype (variable expressivity in dogs with one or two copies of the mutation). The development of the CMO disease is dependent on the genotype but obviously influenced by other unknown genetic and/or non-genetic (environmental) factors. The mutation that we have identified may work in conjunction with unknown 'modifier' mutations in the three studied dog breeds. These modifier mutations would be harmless on its own, but are disease-exacerbating when inherited along with the CMO mutation. We speculate that the modifier mutations are quite common, and it is therefore rare for dogs to have two copies of the CMO mutation and to be free of the modifier mutation, and as a result, to be clinically free from CMO.

The results of our research suggest that there may be other causes of CMO in the breeds so we cannot exclude the formal possibility that carriers could develop a genetically different form of CMO due to other mutations that are not detected by this test.

DNA test

Because of the diagnostic value of the identified mutation, a direct DNA test for CMO will be launched on the 1st December 2012 and will be priced at EUR 85. Full details are available from our website: http://www.genetics.unibe.ch/content/service/dog/index_eng.html

The test will be based on the CMO causing mutation we have identified and will accurately provide the genotype of Cairn terriers, Scottish terriers, and West Highland White terriers. Results will be explained as follows:

CMO-0 (clear): These dogs have two normal copies of DNA and are highly likely to be clear of CMO.

CMO-1 (low risk): These dogs have one copy of the CMO mutation and one normal copy of DNA. These dogs are at low risk to develop CMO themselves as a result of the CMO mutation and they will pass the mutation on to approximately 50% of their offspring. The other 50% of their offspring will receive a normal copy of the gene. If these animals are bred with a clear (CMO-0) partner, half of the puppies will be CMO-1 (low risk), the other half will be CMO-0 (clear).

CMO-2 (high risk): These dogs have two copies of the CMO mutation and have a high chance of developing CMO (more than 57 % of dogs studied in our research program with two copies of the CMO mutation were clinically affected with CMO). Veterinarians and breeders should be aware that the CMO-2 genotype is not completely penetrant. CMO-2 dogs will transmit one copy of the mutant gene to all their offspring.

The test will effectively reduce the number of CMO cases in the affected three terrier breeds. We strongly discourage to breed with CMO-2 dogs. CMO-1 dogs may be still used in breeding, if they are mated with homozygous CMO-0 (clear) dogs. A strict exclusion of all CMO-1 dogs would narrow the restricted gene pool of the affected breeds too much. This might lead to an increase of other hereditary diseases. Valuable CMO-1 breeding dogs should be used at the moment and will have 50% free offspring, if they are mated to CMO-0 animals. The free offspring can then be used to select the best dogs with the desired traits for the next generation.

We particularly encourage owners of clinically affected dogs to submit samples. Blood samples from affected dogs that are submitted together with the X-rays, will be tested free of charge. This information will help us to evaluate the penetrance level of the mutation, to possibly refine the risk prediction in the future if necessary and to start to investigate possible additional cause(s) of CMO in the three terrier breeds.

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