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Genetics of elbow dysplasia

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INTRODUCTION

Elbow dysplasia (ED) is the most common heritable disease causing front leg lameness in dogs (Grøndalen & Lingaas, 1991; Hayes et al., 1979; Mason et al., 1980). ED includes different types of growth disorders: ununited anconeal process (UAP), osteochondritis dissecans of the medial humeral condyle (OCD), fragmented medial coronoid process (FCP), and incongruity of the elbow joint (INC). FCP is prevalent in several dog breeds. Purebred dog populations represent genetically closed populations. In case the genetic risk factor has a recessive or polygenetic inheritance pattern, has a variable pattern in penetration, or is based on a genetic diseases with a high influence by environmental aspects then, especially when manifest at older age, the entity has all chances to spread around in the population before being recognized (Ubbink, 1998; Patterson et al., 1989; Parker et al., 2004).

POPULATION GENETICS

FCP is seen in many breeds and in large percentages, up to 50% of the screened population (Swenson et al., 1997; Ubbink et al., 1999). The heritability estimates (£h^2$) are between 0.24-0.43 for Bernese Mountain dogs, 0.77 for Labradors and 0.45 for Golden Retrievers (Guthrie and Pidduck, 1990). For Retrievers, these figures are for OCD plus FCP, and thus found to be polygenetic in addition to multifactorial (Padgett et al., 1995), although there is enough evidence to conclude that FCP and OCD are two different, independently inherited entities (Janutta et al., 2006). In Labrador retrievers, FCP is more prevalent in male than in female dogs. The ratio of affected males to females varied from 2:1 to 5:1 in different studies (Grøndalen & Lingaas 1991; Guthrie & Pidduck 1990; Guthrie et al. 1992; Hayes et al. 1979; Padgett et al. 1995; Studert et al. 1991).

It has been shown in Swedish breeding programs that based on massive screening for ED and open registration of the results, the prevalence of osteoarthrosis (OA) due to ED decreases due to a decrease in incidence of the primary causes of OA (Swenson et al., 1997). It has been firstly shown in Sweden that the screening protocol and control program can reduce the existing of ED from 60% to 38% in Bernese Mountain dogs and 60% to 45% in Rottweiler population. The reduction of prevalence of ED had advantages over overall cost spented by breeders (Swenson et al., 1997). The screening program for ED has also established in other countries since then in a limited amount of breeds (Ubbink et al., 1998; Remy et al., 2004; Turner 2007), however the decrease in incidence of ED plateaus at a certain level. This can partially be explained by the finding that FCP in Labradors follows the hereditary pattern of a variability in expression of a major, dominant gene; the penetration of FCP in males is 70% and in females is only 28% (Everts, 2000). For breeders this is important information, since it warrants not only the screening of the breeding stock, but also of related animals (i.e. littermates) and offspring, which might tell more about the genetic make-up of a particular dog than the radiograph of its own elbow joints.

Cluster analysis of one breed, using computerized programs containing all pedigrees of the investigated population, reveals histograms representing a group of related dogs with 1/8th of the genome in common. We evaluated Labrador Retrievers, Bernese Mountain dogs and Golden Retrievers in groups, non-selectively chosen from the Dutch population and representative for that population (Ubbink et al., 1999, 2000; Dijkshoorn et al., 2005). Certain related groups revealed members positive for FCP in 27-50% of the related dogs. These positive dogs are spread over the country so the environment (i.e., housing, rural vs town area) are different in many cases. In Labradors and Goldens the affected groups were quite related and less related with non-affected groups; in Bernese Mountain dogs however, all groups of 1/8th-related dogs (i.e., 1/8th of the genome in common) were affected with ED and all groups were connected which each other at the 8th generation (born just after 1945).

MOLECULAR GENETICS

Since FCP is unique in the canine species, it is unlikely that alleles mapped in other species may be of help to identify the responsible gene(s). However, it has been found that a major part of bone dysplasia disorders in man are due to unique mutations in genes coding for collagen proteins (Kuivaniemi et al. 1997a; Mundlos et al. 1997 a). Recently we published a study where we evaluated a number of collagen genes that are...
involved in human bone dysplasias as candidate genes for FCP in Labrador retrievers (Salg et al., 2006). The gene coding for 14 collagen types were selected as candidate genes. However, none of the analyzed collagen genes is likely to play an important role in the etiology of the disorder.

We studied a large group of Labradors with known radiological determined elbow status screened with at least four views per elbow joint (Voorhout et al., 1987), at the age of 14±2 months of age. The genome of Labradors originating from the same litters with and without FCP were compared and studied by sib pair analysis, but this did not result in detection of significant differences between groups (Everts, 2000).

Subsequently genome-wide scan linkage analysis has been conducted with more than 300 polymorphic microsatellite markers and with more than 1500 SNPs revealing a possible FCP-locus (Salg et al. 2006, Temwichit et al., in preparation). Fine mapping of the possible FCP-region with an additional 380 SNPs elucidated three candidate genes, although association of dense SNPs along a segment of 16 Mb is still necessary to identify the FCP-affected allele(s).

High density mapping and association studies may stimulate the molecular genetic studies in elbow dysplasia. Eventually, it is to be expected that DNA-analysis of the population as part of a screening programme for ED, will detect dogs with the affected gene(s) which did not express the disease (due to optimal environmental circumstances or due to variance in penetrance) or dogs heterozygous for the disease.

CONCLUSION
Detection of the FCP-allele(s) will allow us to study the etiopathogenesis of the disease and make it perhaps possible to develop a specific strategy to prevent or cure the disease. DNA-analysis of the potential breeding stock will forestall a lot of frustration for breeders who now experience affected offspring of phenotypic normal parent dogs and thus a slow decrease of the incidence of these hereditary diseases in next generations.

The difference in presentation of FCP in for example Labradors versus Bernese Mountain dogs suggests a difference in pathogenesis and genetic involvement between breeds. It is the responsibility of each association of breeders which is involved in this painful and disabling disease in a significant percentage of dogs in future generations, to initiate molecular genetic research and provide funding for these time consuming and expensive studies.

REFERENCES


