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Review

The long (and winding) road to gene discovery for canine hip dysplasia

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Abstract

Hip dysplasia is a common inherited trait of dogs that results in secondary osteoarthritis. In this article the methods used to uncover the mutations contributing to this condition are reviewed, beginning with hip phenotyping. Coarse, genome-wide, microsatellite-based screens of pedigrees of greyhounds and dysplastic Labrador retrievers were used to identify linked quantitative trait loci (QTL). Fine-mapping across two chromosomes (CFA11 and 29) was employed using single nucleotide polymorphism (SNP) genotyping. Power analyses and preferential selection of dogs for ongoing SNP-based genotyping is described with the aim of refining the QTL intervals to 1–2 megabases on these and several additional chromosomes prior to candidate gene screening. The review considers how a mutation or a genetic marker such as a SNP or haplotype of SNPs might be combined with pedigree and phenotype information to create a 'breeding value' that could improve the accuracy of predicting a dog's hip conformation.
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Introduction

Canine hip dysplasia (CHD) is a common inherited orthopedic trait. This joint malformation (dysplasia) results in instability and subluxation of the hip which ultimately causes erosion of the articular cartilage and synovitis. This secondary osteoarthritis (OA) precipitates the clinical signs of lameness. The disease affects dogs of all breeds with different prevalence. Breed occurrence, as estimated by the Orthopedic Foundation for Animals (OFA), varies widely from 1% to 75%.[4]

For many years, veterinarians have relied on a phenotypic assessment of the hips of dogs based on radiography (Lust, 1997). This method of diagnosis can be combined with a clinical examination to make treatment decisions but is not a reliable method for eliminating affected dogs from a breed or for selecting dogs with the most resistant genetic composition for breeding because hip dysplasia is a complex or quantitative trait. A quantitative trait locus (QTL) is a region on a chromosome that contains a gene or group of genes that influences the phenotypic expression of a quantitative trait like hip dysplasia. Particular alleles in sufficient number have to be encoded in a dog's DNA and expressed during hip development to produce resistance

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[4] See: http://www.offa.org/hipstatbreed.html.

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or susceptibility to the trait. Environmental or non-genetic factors then exert their influence to maximize or minimize the phenotypic expression of the trait, as observed in pelvic radiographs in the case of hip dysplasia.

A phenotypically normal dog can carry mutations that influence trait expression. Two approaches to the screening for, and diagnosis of, CHD have evolved over the last 15–20 years, namely, radiographic detection through the development of novel imaging techniques, and genetic mapping experiments. For a complex trait like CHD, objective hip measurements are usually correlated with each other at the phenotypic level (Lust et al., 2001a; Farese et al., 1998; Puerto et al., 1999; Todhunter et al., 2003a, 2003b, 2003c). Studies have indicated that the estimates of heritabilities and breeding values (BVs) derived from a multiple-trait model, which incorporated both genetic and environmental correlations, would be more accurate than if estimates were derived from a single trait (Jiang and Zeng, 1995; Sapp et al., 2005). More importantly, the genetic parameters estimated from a multiple-trait model provide the essential parameters to derive a selection index that integrates the BVs of all the traits (Ohlerth et al., 2001). Genetic mapping is the process of locating a region on a chromosome that harbours a genetic locus that contributes to, or causes, an inherited trait. Subsequent studies aim to discover the contributing mutations within those chromosomal regions.

The concept is to find the genes that contribute to hip dysplasia and to use molecular markers near these contributing genes or the genetic mutations themselves to identify susceptible or resistant dogs. This information is then used in conjunction with radiographic hip screening on a pedigree to derive BVs that could be applied in breeding programs or registries to reduce the incidence of the trait. These BVs and genetic marker information could be used by purchasers of purebred puppies to assess the potential orthopedic health of the animal. Genetic marker information would be particularly helpful in this context as the purchaser would have no information on the offspring of that individual.

This paper reviews recent developments in CHD genetic locus mapping and assesses how phenotypic and genotypic information can be used to reduce the incidence of this condition.

Canine hip dysplasia phenotype

Radiology has commonly been used to diagnose CHD. The technique has been standardized worldwide, although there is some variation in radiograph evaluation (Flückiger, 2007). There are three (somewhat different) international scoring methods: the Fédération Cynologique Internationale (FCI), the OFA, and the British Veterinary Association/Kennel Club (BVA/KC) methods. The FCI scoring method is used in most mainland European countries, Russia, South America, and Asia. The OFA approach is used exclusively in the USA and Canada, and the BVA/KC method is used in Britain, Ireland, Australia and New Zealand. Details of each scoring method are described by Flückiger (2007).

The North American method of assessing hip conformation is the extended-hip radiographic score of 'excellent', 'good', and 'fair' with 'borderline', 'mild', 'moderate' and 'severe' hip dysplasia as developed by the OFA and is one of the methods used in our studies (Fig. 1). The Norberg angle (NA) (Gustafsson et al., 1975) is measured from the ventrodorsal, extended-hip radiograph and ranges from 50° (a subluxated hip) to 123° (a phenotypically unaffected hip) in our database. The maximum amount of lateral hip laxity is measured as the distraction index (DI) on a radiograph taken in the distraction position (PennHIP) (Smith et al., 1997). Labrador retrievers with DIs < 0.4 at 8 months of age have a $>80\%$ probability of not developing secondary hip OA (i.e. were unaffected with hip dysplasia). Those retrievers with DIs >0.7 had a high probability of developing hip OA (Lust et al., 1993). The PennHIP scheme also requests submission of a ventrodorsal extended-hip radiograph used to assess hip conformation and the presence or absence of secondary OA. In the absence of trauma, the presence of secondary hip OA is considered the 'prior footprint' of CHD. The dorsolateral subluxation (DLS) score is the percentage of the femoral head covered by the dorsal acetabulum with the hips in a natural weight-bearing position (Farese et al., 1998; Burton-Wurster et al., 1999; Lust et al., 2001a, 2001b). This score ranges from 85% for tight-hipped greyhounds in our database to 21% for the most dysplastic dogs. Both the DI and the DLS scores are repeatable (Farese et al., 1998; Smith et al., 1997).

Additionally, for a group of Labrador retrievers, greyhounds, and their crossbred offspring, reared in a controlled environment, the DLS score and Norberg angle together better predicted whether an affected hip would develop OA at early maturity than did the DLS or DI score or the NA in isolation (Todhunter et al., 2003b). Although these three radiographic measurements are highly correlated (Farese et al., 1999; Lust et al., 2001a; Todhunter et al., 2003b), no one of them exactly represents the other two. One way of integrating these traits measured on the left and right sides was to derive their Principal Components (PC). For the eight measurements (four traits on both hips of each dog), there could be eight PCs at most. However, the first PC usually contains the most information by explaining the greatest amount of variation. Another important feature of PCs is the lack of correlation between them. The second PC is orthogonal to the first and defines the next largest amount of variation and is independent of the first PC.

For a subset of 850 dogs in the Cornell hip dysplasia archive, the first four PCs calculated from the eight measurements (OFA score, the DI, the DLS score, and the NA measures of left and right hips) explained 50%, 16%, 15% and 11% (92% total) of the total variation in the CHD phenotype, respectively. The highest correlation was between the DI and DLS score (50%). The second highest degree of correlation was between the NA and