Etiopathogenesis of Canine Hip Dysplasia, Prevalence, and Genetics

Michael D. King, BVSc, MS

KEYWORDS

• Pathogenesis • Genetic • Dysplasia • Prevalence

KEY POINTS

- Canine hip dysplasia is the most common orthopedic condition diagnosed in the dog, with prevalence of up to 71% in affected breeds.
- As a polygenic genetic disease, it has a complex mode of inheritance, with phenotypic expression affected by external factors.
- Joint laxity leads to abnormal wearing of the coxofemoral joint and subsequent osteoarthritis.
- Although some specific genes that contribute to hip dysplasia have been identified, the basis for hip dysplasia consists of many genes each contributing a small effect.

INTRODUCTION

First described in 1935 by Schnelle, canine hip dysplasia (CHD) is considered to be the most common orthopedic condition diagnosed in the dog.[1–7] As most patients have only mild clinical signs associated with CHD, it is possible, however, that cranial cruciate ligament rupture is a more common cause of hind limb lameness.[8,9] Even in dogs with only minor radiographic evidence of CHD, a change in gait is often present despite the lack of an obvious lameness.[10]

CHD has a genetic basis, although with a polygenic or complex mode of inheritance. Multiple environmental factors modify the expression of this predisposition, affecting the way it manifests, and its severity.[1,2,4,5,11–15] Although seen in a variety of breeds, CHD is most prevalent in large, fast-growing dogs, with Labrador retrievers, Newfoundlands, rottweilers, St. Bernards, and mastiffs commonly affected. Bulldogs, pugs, and some terrier breeds are also very predisposed.[3–5,16]

Disclosure: The author has nothing to disclose.
Department of Surgery, Canada West Veterinary Specialists & Critical Care Hospital, 1988 Kootenay Street, Vancouver, British Columbia V5M 4Y3, Canada
E-mail address: mking@canadawestvets.com

Vet Clin Small Anim 47 (2017) 753–767
http://dx.doi.org/10.1016/j.cvsm.2017.03.001 **vetsmall.theclinics.com**
0195-5616/17/© 2017 Elsevier Inc. All rights reserved.

CAUSE

The exact cause of CHD remains unknown, although it was defined by Henricson in 1966 as "a varying degree of laxity of the hip joint permitting subluxation during early life, giving rise to varying degrees of shallow acetabulum and flattening of the femoral head, finally, inevitably leading to osteoarthritis."[14] The phenotypic expression of a genetically predisposed dog is joint laxity, which is the focus of both early diagnostics and traditional screening techniques, as well as some surgical treatment methods in young patients.[1–4,17,18] However, joint laxity alone, although necessary, does not seem to be sufficient in isolation for the development of CHD.[19,20] There appears to be significant breed and individual variation in the tolerance of a specific degree of joint laxity, and both the rate and the incidence of subsequent development of osteoarthritis (OA).[20–22]

Although CHD is considered (by definition) to be a disease of the coxofemoral joints, there is evidence that this may be the most visible aspect of a more generalized disease in predisposed dogs. It is known that puppies that develop with excessive joint laxity in the hips have a high risk of developing OA in those joints later in life.[1,3,17,19,23,24] However, they are also at increased risk of developing OA of the shoulder, and potentially other joints, including the elbow, stifle, vertebra, and mandibular joint.[4,25] One study identified increased cartilage weights, and increased fibronectin content of cartilage sampled from the humerus in dogs with CHD, which are thought to be early indicators of OA.[26]

PATHOGENESIS

Dogs predisposed to CHD are born with normal hips that subsequently become dysplastic, exhibiting increased joint laxity. The reason for this remains unclear, although abnormalities in endochondral ossification and acetabular development are also thought to be involved.[1,27]

Joint Laxity

Passive hip joint laxity is that which is able to be measured by palpation or sedated radiograph and may be tolerated by individuals without any apparent dysfunction. Functional laxity is the pathologic instability that actually occurs during weight-bearing, resulting in subluxation of the femoral head and abnormal forces across the joint. It cannot be measured directly, and passive laxity is used as an approximation.[1,3,28]

Primary anatomic stabilizers of the coxofemoral joint include the ligament of the head of the femur, the joint capsule, and the dorsal acetabular rim.[29] The synovial fluid, in combination with the joint capsule, also provides a powerful stabilizing effect.[5,23]

The ligament of the head of the femur has been shown to be abnormal and thickened in dogs with dysplastic hips exhibiting moderate to severe OA.[30] A later study however showed no such difference in the volume of the ligament in dogs with mild OA.[31]

Joint stability in neutral positions is maintained in large part due to atmospheric pressures, through the vacuum phenomenon within the joint itself.[3,23] A close association has been demonstrated between the volume of synovial fluid present and the degree of laxity within the hip, with increased fluid resulting in more pronounced laxity, and vice versa.[4,32] Increased joint fluid volumes have been confirmed within the coxofemoral joints of dogs exhibiting CHD, which has led to some suggestion that hip laxity could be secondary to excessive synovial fluid quantities. The fact that this

volume (as measured by the distraction index [DI]) remains constant through early periods of development is surmised by some investigators as evidence of this.[1,4,23]

Synovial fluid is mainly created through dialysis of blood within the intracapsular vessels, with plasma modified by vascular endothelium, connective tissue, and synoviocytes. There are no known active homeostatic mechanisms in synovial fluid regulation, with removal through intracapsular veins and lymphatics maintaining a balance.[23] Inflammatory processes can affect this balance, with leakage of proteins into the joint and decreasing drainage. In addition, as intraarticular pressure increases, synoviocytes decrease in size, which enlarges intercellular gaps, contributing to greater permeability of the joint capsule, further increasing joint fluid accumulation.[23,31] These factors make it uncertain if increased joint fluid within the coxofemoral joint of a dog with CHD is a primary cause of joint laxity, or if it is simply synovitis as a result of that laxity.

The mechanical strength of the joint capsule is determined by its collagen content, something that is known to be abnormal in people with hip dysplasia. One study investigated the ratio of type III:I collagen in coxofemoral joint synovium, with a high ratio indicating a weak joint capsule, because type I collagen is needed for strength. This study showed an increased ratio in breeds predisposed to CHD compared with greyhounds, although no difference between dysplastic and nondysplastic dogs in each group.[33] A follow-up study assessed the same ratio in the umbilical tissues of newborn puppies, which showed no difference between dysplastic and nondysplastic dogs.[23] The investigators concluded that this did not support a primary, generalized alteration in collagen composition in dysplastic dogs.

Subluxation

Traditionally it has been thought that subluxation occurs with weight-bearing (functional laxity), and the femoral head in a dysplastic hip then translates laterally. The muscle forces acting around the hip increase, whereas the contact area within the hip decreases, resulting in incongruence and abnormal wearing of articular cartilage.[1,3,19]

An alternative theory has been proposed to explain the pathogenic mechanism of joint laxity causing joint degeneration in dogs with CHD; the investigators surmise that subluxation is occurring during the swing phase of the gait, rather than upon weight-bearing. With normal (low) levels of synovial fluid, any lateral translation of the femoral head during the swing phase of ambulation would result in invagination and stretching of the joint capsule. Mechanoreceptors within the capsule would then be triggered, recruiting adjacent muscles to contract in a protective role, positioning the femoral head closer to the acetabulum. With increased synovial fluid present, it would theoretically take more pronounced subluxation of the femoral head during the swing phase to trigger the same stretch response and muscle recruitment. Upon weight-bearing, the hip would be positioned in a progressively more subluxated orientation, leading to sudden and damaging reduction of the hip.[1]

Although not proven, their justification of this lies in the distribution and action of muscles around the hip. During weight-bearing, several powerful muscles (specifically the gluteals and adductors), oriented largely perpendicular to the joint, act together providing a strong resolved force directing the femoral head into a reduced position within the acetabulum. In contrast, during the swing phase, the muscles involved in advancing the limb (iliopsoas, rectus femoris, sartorius) produce a weaker force, but oriented parallel to the femur, creating a net vertical load that predisposes to hip subluxation. In addition, the investigators propose that if subluxation and abnormal wearing occurred during weight-bearing, cartilage damage would be focused more

cranially in the femoral head and acetabulum, in line with the strongest propulsive forces. They note that the characteristic location and distribution of cartilage wear are immediately dorsal to the fovea capitis, suggesting it is "catastrophic reduction" of the femoral head upon weight-bearing causing joint degeneration.[1]

Alterations in endochondral ossification in the developing pelvis have also been proposed as a contributor to CHD.[2] The acetabulum forms between the ventral arms of the shared physis of the ilium, pubis, and ischium, known as the triradiate growth plate. A secondary acetabular ossification center then forms within the physis itself before closure at 4 to 5 months of age, whereas the capital physis closes between 9 and 11 months of age. Closure of the femoral capital physis has been shown to be delayed in dysplastic dogs, as is the onset of ossification of the femoral head.[2,34] This is thought to be due to compressive weight-bearing forces applied to the medial aspect of the femoral head and dorsal rim of the acetabulum interfering with normal ossification.[4]

Biomechanical factors associated with bone conformation in the pelvis have been proposed as contributing factors to CHD. Although femoral angle and degree of anteversion do not appear to have an effect, a steeper or more pronounced acetabular slope has been associated with subluxation.[19] This makes sense given the dorsal acetabular rim's role as a primary hip stabilizer, although it is uncertain if an increased acetabular slope is a primary factor, or if it occurs secondary to interference with normal hip development caused by joint laxity and abnormal wearing.

Lumbosacral abnormalities have also been shown to be somewhat associated with development of CHD, presumably due to the proximity to the developing pelvis.[35]

Normal force, congruency, and load are needed between the femoral head and acetabulum in order for the coxofemoral joint to develop correctly.

With hip subluxation, there is a concentration of mechanical load on the dorsal acetabular rim that may act to slow cartilage growth and development. The period of maximal growth and hip development occurs between 3 and 8 months of age in dogs, and abnormal forces at this age in a dysplastic hip are thought to have a critical effect on the expression of CHD in predisposed dogs.[2,3,19,36] Radiographic evidence of hip laxity can be seen as early as 2 months of age (although this has not always been shown to be strongly associated with development of CHD), with signs of OA identified sometime after 4 to 6 months of age.[3,14,22,28,32] Assessment of hip subluxation on a hip-extended ventrodorsal view radiograph has been the traditional method of diagnosis of CHD, with it the thought that dogs with apparently normal conformation by 2 years of age did not go on to develop significant degenerative joint disease. This has since been shown to be somewhat inaccurate, at least in part due to the technique's positioning artificially improving joint tightness. The DI radiographic technique has demonstrated accurate prediction of susceptibility to OA due to CHD, confirming joint laxity as the precursor to degenerative joint disease.[3,5,17,37]

Development of Osteoarthritis

Although hip laxity and subluxation in young dogs with CHD are seen to cause lameness in some individuals, it is the development of OA secondary to this laxity (or potentially with contribution from a separate genetic effect distinct from expression of CHD) that causes the most morbidity.[3–5,21] Development of OA has traditionally been described as a biphasic, seen most often before 2 years of age, and then again when geriatric, but is now thought to progress with a more linear incidence as dogs age.[3]

Clinical signs are seen in juvenile dogs with tearing and inflammation of the joint capsule, as well as microfracture of the dorsal acetabular rim.[1,4,38] In response to

this damage, periarticular fibrosis forms and is associated with a decreased incidence of clinical signs. It was initially thought that the fibrosis results in increased joint stability, although this is questionable, with a more recent study demonstrating increasing laxity with progression of OA.[39]

Whatever the exact mechanism, hip laxity and subluxation result in incongruence of the coxofemoral joint, and increased force acting over a smaller contact area. This causes abnormal wearing of the cartilage, and microfractures of the dorsal acetabular rim.[1,4,38] The degree of laxity and remodeling present at 6 months, as assessed by the reduction angle of the hip, have been shown to be a strong predictor of OA development at 2 years of age.[19]

Initial stress on articular cartilage results in release of destructive enzymes from chondrocytes, synoviocytes, and inflammatory cells that degrade matrix proteoglycans.[40] Water content within the cartilage increases, and damage to underlying collagen structure occurs, leading to fibrillation and decreased cartilage stiffness, making it more susceptible to injury.[31,38,40] Because of this biomechanical change, the cartilage is subjected to increased strain (greater deformation when a load is applied) and is less able to return to its normal shape once the load is released.[38] Inflammatory cytokines, such as inerleukin-1 (IL-1), IL-6, and tumor necrosis factor, are known to be involved in this process and have been confirmed to be present in increased amounts in the hips of dysplastic dogs.[31,41]

Microfractures and stress on the subchondral bone occur due to abnormal weight-bearing on the femoral head and dorsal acetabular rim. As it remodels and heals, the bone at both sites becomes denser and less able to absorb shock. A larger amount of the weight-bearing force is then transmitted to the overlying cartilage, accelerating degeneration.[2,4,42]

Synovial fluid loses some viscosity due to lower hyaluronan content, which decreases joint lubrication. Fragments of damaged cartilage worsen the inflammatory response, creating further chondrocyte loss.[40]

Proliferation of chondrocytes occurs, in an attempt to compensate for damage. They form clusters of cells, often at the edge of the lesion.[2] This cartilage synthesis is associated with greater cartilage thickness, due to tissue swelling as well as an increase in both number of cells and amount of extracellular matrix. Although there is initially an upregulation of degradation and synthesis processes, eventually the cartilage is unable to maintain its repair processes, and chondrocyte loss occurs.[4,23,31]

Subchondral bone becomes exposed, resulting in yet further inflammation. Through weight-bearing and remodeling, it becomes sclerotic and eburnated with a polished appearance.[4,38,40] Focal subchondral bone necrosis occurs, thought to be due to heat caused by friction or repeated microfracture.[38]

Continued inflammation and abnormal wearing create additional loss of normal joint conformation. The acetabulum becomes shallower and wider, whereas the femoral head flattens.[1,4,38] Increased stress and inflammation of the synovium result in tearing of Sharpey fibers at the insertion of the joint capsule, which sees the formation of osteophytes.[4,38,40] Mesenchymal stem cells within the periosteum or synovial lining are thought to be the precursors of true osteophytes at the joint margin,[40] with cytokines of the transforming growth factor-beta family (TGF-ß) also involved in the induction of osteophytosis. Injection of TGF-ß into experimentally normal joints has resulted in osteophyte formation, and its expression has been identified in osteophytes from both people and animals with OA.[31]As osteophytosis and bone remodeling progress, the characteristic radiographic appearance of thickening of the femoral neck and proliferation of the dorsal acetabular rim is seen.[4,5,38]

OA is an irreversible outcome of CHD and can be extremely debilitating. Although most dogs with CHD exhibit no or only mild clinical signs, its high prevalence makes it a very serious problem, especially as many of the breeds commonly affected are highly trained working and service dogs.[4,43] Because there is no definitive therapy for OA, improving patient welfare requires better understanding of the genetic basis of CHD, it is hoped, to decrease the prevalence in affected breeds through selective breeding.[4,12,43]

GENETICS

Two factors determine the expression of CHD in a dog: genetic predisposition and environment. An individual's phenotype (whether they exhibit hip laxity and CHD) is determined by its genotype in combination with influencing external environmental factors.[2,4,12]

Heritability

The degree to which the expression of a condition is explained by its genotype is quantified by the estimate of the trait's heritability, which is designated by the symbol h^2. Heritability is defined as the ratio of additive genetic variation:the overall phenotypic variation of a given trait ($h^2 = V_g/V_p$).[4,12] Therefore, a heritability of 1.0 indicates that the occurrence of the trait is entirely controlled by the presence or absence of a gene, regardless of any environmental factors. A heritability of 0.0 means the trait is not genetically influenced. CHD is a polygenic trait, influenced by environmental effects.[4,12] Polygenic inheritance implies a large, but unknown number of alleles involved, scattered throughout the genome.[44,45]

The heritability of CHD has been estimated between 0.1 and 0.6, with most values decreasing to less than 0.5.[2,4,11,12,43,44,46] A large study assessing hip scores for Labrador retrievers in the United Kingdom identified heritability of 0.34 from the parents, with 0.41 from the sire alone and 0.3 from the dam alone.[46] A study of more than 1700 boxers from 325 litters identified a heritability of only 0.11 for development of clinical signs of CHD.[43] Two early studies assessing German shepherds identified heritability estimates of 0.22 and 0.43 for subjective hip scores.[12] A more recent investigation of 4 less common breeds found the pooled heritability for hip scores in English setters, Portuguese water dogs, Chinese shar peis, and Bernese mountain dogs as 0.26.[47]

These estimates would be considered to show low heritability, because any genetic change would be slow with selective breeding.[12]

As heritability is specific to the population of dogs being investigated, it is also specific to the trait being assessed.[11,12] Coxofemoral joint laxity has been shown to demonstrate higher levels of heritability than hip scoring. Heritability estimates for laxity of 0.46 in German shepherds and Labrador retrievers, 0.64 in golden retrievers, and 0.85 in Estrela mountain dogs have been described.[11,12] A study that assessed dogs from 17 different breeds identified heritability estimates of 0.61 for the DI and 0.73 for the Norberg angle.[48] This is important, because the higher the heritability of a trait, the greater the expected genetic improvement over time from selective breeding.

Selection Pressure

Breeding parents with a phenotype that is better than the average for the population overall exerts a selection pressure on the progeny. The selection pressure is determined as the difference between the average phenotype of the parents and the

average phenotype of the population. The expected genetic change, or improvement in average phenotype of the progeny (ΔG), can be calculated as follows:

$\Delta G = h^2 \times (Average_{parents} - Average_{population})$

The amount of genetic change expected is therefore dependent on the heritability of the trait, and the amount of selection pressure able to be applied.[12] As an example, if one considers the DI in a breeding pair and assumes a heritability of 0.25, with a parental average of 0.2, and a population average of 0.6, the following formula results:

$\Delta G = 0.25 \times -0.4$

$\Delta G = -0.1$

Thus, the low heritability in this example leads to only 25% of the selection pressure being applied and results in a slow rate of genetic improvement. In addition, as the difference between the population average and the average of the selected parents becomes less pronounced with each generation, the amount of selection pressure able to be applied decreases. Therefore, progress over time becomes more incremental as prevalence decreases.[4,11,12]

Traditional selective breeding schemes have used hip scores based on the ventrodorsal extended-hip-view radiograph, with in general only slow genetic improvement shown over time.[1] A study of German shepherds in Finland showed no genetic improvement when using subjective hip scores as criteria.[49] Assessment of the progress of 6 breeds within the UK screening system showed no significant improvement in genetic progress over 13 years, and in the case of the Siberian husky, the hip scores had in fact worsened slightly.[50] A more recent investigation of UK dogs also identified a worsening genetic trend for CHD in the Siberian husky.[43] Because the husky has traditionally had extremely good hip scores, it is hypothesized that as a sled dog the breed had undergone selection against lameness (including CHD), but with increasing popularity as a pet and as show dogs, that this selection pressure may have weakened.

A US study of dogs assessed through the Orthopedic Foundation for Animals (OFA) scoring system identified significant improvement in hip scores.[51] An investigation of specifically Labrador retrievers within the OFA system also identified improvement over time, although it was minimal. This study identified a low heritability of only 0.21, which may explain the slow progress.[52]

Applying selection pressure based on other traits with higher heritability, such as DI, or dorsolateral subluxation would be expected to improve the rate of genetic improvement.[1,11,37]

Alternatively, the use of estimated breeding values (EBV) has been recommended to achieve even faster genetic progress.[1,11,12,44,48,53] An EBV is an assessment based on an individual's pedigree, derived from the hip quality of relatives and offspring. It is a more precise determination of a dog's genetic quality than individual records alone.[11] The EBV is calculated on a trait-by-trait basis for each dog and calculated to obtain a best linear unbiased prediction of a dog's relative genotype.[44,48] This calculation is then used to compare dogs for more accurate selection as potential breeding. Although time intensive, it has been shown to result in more rapid genetic improvement, with one study showing a decreased incidence of CHD in German shepherds from 55% to 24%, and in Labrador retrievers from 30% to 10%, in less than 5 generations.[44]

Genotyping

As with any inherited disease, the ideal technique for selective breeding and diagnosis would be a genetic test for the mutations that cause CHD. Inheritance of specific traits associated with CHD has been described, including femoral capital physeal

ossification, DI, and subluxation score.[54] Unfortunately, because of the complex nature of the underlying genetics, progress in identifying specific genes or markers has been slow.[1,55,56]

A region on a chromosome that contains a gene or group of genes that influences the phenotypic expression of a quantitative trait such as CHD is referred to as a quantitative trait locus (QTL).[1,55] Several QTLs have been identified on several chromosomes, including on canine familiaris autosomes (CFAs) 01, 03, 04, 08, 09, 16, 19, 26, and 33,[57] and CFAs 04, 09, 10, 11, 16, 20, 22, 25, 29, 30, 35, and 37.[58] The identification of QTL in several studies in a variety of breeds suggests that at least 1 QTL on each of several chromosomes (CFAs 01, 04, 09, and 16) affects hip joint conformation.[59]

A specific QTL associated with acetabular osteophyte formation secondary to CHD in Portuguese water dogs has been identified on CFA 03.[60] This is thought to be evidence of QTLs that regulate the severity of secondary hip OA separately from those involved in expression of CHD.[21]

Recently, a fibrillar 2 gene haplotype (FBN2) was identified on CFA 11 associated with CHD. Dogs with the deletion haplotype exhibited significantly worse CHD as measured via DI, Norberg angle, extended hip radiograph, and dorsal subluxation score. FBN2 encodes for a component of extracellular matrix that is present in joint capsule and articular cartilage. Mutations of this gene have been associated with joint laxity in people.[61]

Only a small portion of the complex genetic basis for CHD has been determined so far and appears to consist of many genes that each contribute a small or moderate effect. This suggests that genomic selection, rather than specific marker-assisted selection, may be the most effective strategy for decreasing CHD prevalence.[62] There remains optimism that genotyping will eventually allow early intervention and improved selective breeding, and research is ongoing with the goal of developing accurate genetic screening for CHD.[56,63,64]

ENVIRONMENTAL FACTORS

Although an individual may be born with a genotypic predisposition to CHD, that does not automatically result in development of the condition. External factors do not cause hip dysplasia, but they determine whether CHD is expressed, and to what degree (**Table 1**).[4]

Nutrition

Two studies following a cohort of Labrador retrievers in the 1990s showed that limiting food consumption to 75% of that fed to control dogs from 8 weeks of age resulted in a 67% reduction in the prevalence of hip dysplasia at 2 years of age and substantially

Table 1
External factors affecting expression of canine hip dysplasia

Environmental Effects	
Risk factors	Protective Factors
Excessive food consumption	Limited food consumption
Rapid weight gain	Early off-leash exercise
Calcium supplementation	Glycosaminoglycan polysulfates
Dietary anion gap	
Early neuter	

reduced the prevalence and severity of hip joint OA at 5 years of age.[65,66] A follow-up study in 2000 confirmed the prevalence and severity of OA in several joints was less in dogs with long-term reduced food intake, compared with controls.[67]

Rapid weight gain has been determined to be a risk factor in some studies, especially when occurring within the first 6 months.[4,14,65] However, others have found no effect on joint laxity, or expression of CHD.[68,69] One investigation of 4 large breeds in Norway actually identified a protective effect of greater body weight at 3 months of age.[68]

Vitamin C is important in the development of collagen, and supplementing puppies and their dams with high doses was suspected to prevent CHD. There is no evidence that this is effective, and excessive vitamin C can interfere with normal bone and cartilage development. Dogs do not require dietary vitamin C, because they synthesize it themselves, so supplementation is not recommended.[4]

Puppies do not have a mechanism to protect against excess dietary calcium. Supplementing additional calcium or vitamin D results in decreased osteoclastic activity, delaying normal ossification, and can cause CHD in predisposed puppies.[1,2,4,70]

One study assessed the electrolyte balance of the diets fed to 167 dogs during a period of rapid growth. The investigators determined that on average significantly less subluxation of the femoral head was observed when diets with lower dietary anion gap were fed, and this was unrelated to growth rate.[71] This effect on subluxation is thought to be related to a decrease in synovial fluid volume associated with the low anion-gap diets.

Exercise

A correlation between pelvic muscle size and CHD has been described, with less muscle mass seen in dysplastic dogs compared with nondysplastic dogs.[72] Pelvic muscle mass indices (total postmortem mass of pelvic muscle [kg]/body weight [kg] $\times$ 100%) correctly predicted the presence of CHD 94% of the time. The disease was not present if the index was greater than 12 and consistently present when less than 9. Atrophy associated with CHD and early muscle conditioning did not seem to affect the index.

An investigation of risk factors for development of CHD in 4 large breeds in Norway identified that puppies walking on stairs from birth to 3 months of age had an increased incidence. However, they also identified off-leash activity through the same time period as having a protective effect. In addition, birth on a farm and birth in spring and summer resulted in a decreased risk of developing CHD. The investigators proposed that off-leash exercise (and being born into an environment and season that permits that) early in life may result in increased muscle development and strength in the hip area.[13]

The role of exercise in expression of CHD has not been as thoroughly investigated as nutrition, and further research is needed.[4]

Hormones

Several hormones have been proposed as potential contributors to CHD development. Estrogen, relaxin, insulin, and parathyroid hormone have all been investigated.[4] Estrogen administered to puppies has been shown to cause CHD. However, endogenous estrogen levels in dysplastic puppies are no higher than in nondysplastic animals.[1,2,4] Similarly, relaxin given to puppies can promote development of CHD.[1,2,4] Although there is no definitive evidence that endogenous relaxin causes CHD, higher and more persistent levels were identified in a group of lactating Labrador

retrievers when compared with beagles. This finding may suggest an involvement in the higher prevalence of CHD seen in Labrador retrievers.[73]

An investigation of early-age neutering of male and female dogs identified a significant increase in the risk of developing CHD.[15] Assessment of more than 1800 dogs showed that of dogs neutered before 5.5 months of age, 6.7% developed CHD, whereas 4.7% of those neutered at or after 5.5 months of age developed CHD. However, those that were neutered at or after 5.5 months and developed CHD were 3 times more likely to be euthanized for the condition, compared with dogs that were neutered before 5.5 months of age and developed CHD.

Glycosaminoglycan Polysulfates

The only other treatment shown to have an effect on expression of CHD is administration of glycosaminoglycan polysulfates.[74] Twice weekly injections of 5 mg/kg were administered to CHD-susceptible puppies from 6 weeks to 8 months of age. Of the 8 puppies in the treated group, none showed signs of femoral head subluxation at 8 months, whereas 4 of 8 puppies in the control group did.

PREVALENCE

The overall prevalence of CHD in the canine population is unknown. An estimate made at a veterinary teaching hospital based on patients radiographed over a 5-year period determined prevalence within pure-breed dogs as 19.7%, and mix-breed dogs at 17.7%.[75] A more recent study assessed medical records from 27 veterinary teaching hospitals and showed a much lower prevalence of only 3.5%.[76] The investigators noted an increase in prevalence over time in their study but suspect this was due to increased recognition and diagnosis by veterinarians, rather than a true finding.

Prevalence of CHD between different breeds is extremely variable, ranging from 1% for some sighthounds to 71% for bulldogs[16] (**Fig. 1**). Reported prevalence within breeds is also often wide ranging, with numbers for golden retrievers ranging from 9.3% to 73%, and in rottweilers ranging from 11.8% to 53%.[16,76,77] The disparity is attributable to the difficulty in accurately assessing a truly representative sample of the total population, along with differences in prevalence between localized groups resulting in sampling bias.[2,77]

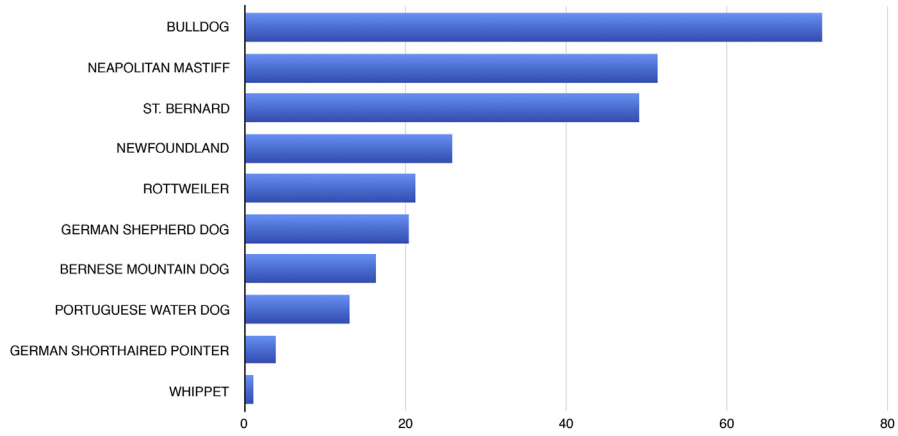

Fig. 1. Prevalence of CHD in a selection of breeds. (*Data from* Orthopedic Foundation for Animals. Available at: http://www.ofa.org/stats_hip.html.)

The only frequently updated and readily available data on CHD prevalence for multiple breeds in the United States is provided by the OFA through their radiographic screening program.[77] Although valuable, these data may underestimate true prevalence. As the OFA does not have a mandatory radiograph submission policy, prescreening by veterinarians is suspected to result in several films with obvious CHD never being assessed.[2,77] In addition, the OFA ventrodorsal radiograph view has been shown to underestimate CHD, and susceptibility to development of OA, when compared with other determinations of joint laxity such as DI.[78]

It is known that in general large and giant breeds have a higher prevalence of CHD, and castrated male dogs have also been identified to be more likely to exhibit the condition.[76] Specific breeds that are known to have a higher risk of CHD include Bernese mountain dog, Chesapeake Bay retriever, German shepherd, golden retriever, Labrador retriever, Newfoundland, old English sheep dog, rottweiler, St. Bernard, and Samoyed.[76,79] Conversely, some breeds identified as being at a lower risk include miniature schnauzer, Chihuahua, Maltese, toy poodle, dachshund.[76]

Despite the challenges in obtaining an accurate assessment of CHD prevalence in the canine population, it is clear that prevalence is unacceptably high in many breeds. Given the lack of effective treatments for resolving CHD once it occurs, continued efforts toward decreasing the prevalence through targeted breeding are needed.[77]

REFERENCES

1. Smith GK, Karbe GT, Agnello KA, et al. Pathogenesis, diagnosis, and control of canine hip dysplasia. In: Tobias KM, Johnston SA, editors. Veterinary surgery small animal, vol. 1, 1st edition. St Louis (MO): Elsevier; 2012. p. 824–48.
2. Krotscheck U, Tohundter T. Pathogenesis of hip dysplasia. In: Bojrab MJ, Monnet E, editors. Mechanisms of disease in small animal surgery. 3rd edition. Jackson (WY): Teton NewMedia; 2010. p. 636–45.
3. Kapatkin A, Fordyce H, Mayhew P, et al. Canine hip dysplasia: the disease and its diagnosis. Comp Cont Edu Pract Vet 2002;24:526–38.
4. Fries CL, Remedios AM. The pathogenesis and diagnosis of canine hip dysplasia: a review. Can Vet J 1995;36(8):494–502.
5. Brass W. Hip dysplasia in dogs. J Small Anim Pract 1989;30:166–70.
6. Lust G. An overview of the pathogenesis of canine hip dysplasia. J Am Vet Med Assoc 1997;210:1443–5.
7. Johnson J, Austin C, Breur G. Incidence of canine appendicular musculoskeletal disorders in 16 veterinary teaching hospitals from 1980 through 1989. Vet Comp Orthop Traumatol 1994;7:56–69.
8. Powers MY, Martinez SA, Lincoln JD, et al. Prevalence of cranial cruciate ligament rupture in a population of dogs with lameness previously attributed to hip dysplasia: 369 cases (1994-2003). J Am Vet Med Assoc 2005;227:1109–11.
9. Banfield CM, Bartels JE, Hudson JA, et al. A retrospective study of canine hip dysplasia in 116 military working dogs. Part II: clinical signs and performance data. J Am Anim Hosp Assoc 1996;32:423–30.
10. Bockstahler BA, Henninger W, Müller M, et al. Influence of borderline hip dysplasia on joint kinematics of clinically sound Belgian shepherd dogs. Am J Vet Res 2007;68:271–6.
11. Ginja MMD, Silvestre AM, Gonzalo-Orden JM, et al. Diagnosis, genetic control and preventive management of canine hip dysplasia: a review. Vet J 2010;184:269–76.

12. Kapatkin A, Mayhew P, Smith G. Genetic control of canine hip dysplasia. Comp Cont Edu Pract Vet 2002;24:681–7.
13. Krontveit RI, Nødtvedt A, Sævik BK, et al. Housing- and exercise-related risk factors associated with the development of hip dysplasia as determined by radiographic evaluation in a prospective cohort of Newfoundlands, Labrador retrievers, Leonbergers, and Irish wolfhounds in Norway. Am J Vet Res 2012; 73:838–46.
14. Richardson DC. The role of nutrition in canine hip dysplasia. Vet Clin North Am Small Anim Pract 1992;22:529–40.
15. Spain C, Scarlett J, Houpt K. Long-term risks and benefits of early-age gonadectomy in dogs. J Am Vet Med Assoc 2004;224:380–7.
16. Hip dysplasia by breed (Orthopedic Foundation Association data). Available at: http://ofa.org/stats_hip.html. Accessed February 2, 2017.
17. Banfield CM, Bartels JE, Hudson JA, et al. A retrospective study of canine hip dysplasia in 116 military working dogs. Part I: angle measurements and Orthopedic Foundation for Animals (OFA) grading. J Am Anim Hosp Assoc 1996;32:413–22.
18. Tsai KL, Murphy KE. Clinical and genetic assessments of hip joint laxity in the Boykin spaniel. Can J Vet Res 2006;70:148–50.
19. Gatineau M, Dupuis J, Beauregard G, et al. Palpation and dorsal acetabular rim radiographic projection for early detection of canine hip dysplasia: a prospective study. Vet Surg 2012;41:42–53.
20. Lust G, Williams AJ, Burton-Wurster N, et al. Joint laxity and its association with hip dysplasia in Labrador retrievers. Am J Vet Res 1993;54:1990–9.
21. Hays L, Zhang Z, Mateescu RG, et al. Quantitative genetics of secondary hip joint osteoarthritis in a Labrador retriever-greyhound pedigree. Am J Vet Res 2007;68: 35–41.
22. Ginja MMD, Ferreira AJ, Jesus SS, et al. Comparison of clinical, radiographic, computed tomographic, and magnetic resonance imaging methods for early prediction of canine hip laxity and dysplasia. Vet Radiol Ultrasound 2009;50:135–43.
23. Madsen JS. The joint capsule and joint laxity in dogs with hip dysplasia. J Am Vet Med Assoc 1997;210:1463–5.
24. Runge JJ, Kelly SP, Gregor TP, et al. Distraction index as a risk factor for osteoarthritis associated with hip dysplasia in four large dog breeds. J Small Anim Pract 2010;51:264–9.
25. Olsewski JM, Lust G, Rending VT, et al. Degenerative joint disease: multiple joint involvement in young and mature dogs. Am J Vet Res 1983;44:1300–8.
26. Farquhar T, Bertram J, Todhunter RJ, et al. Variations in composition of cartilage from the shoulder joints of young adult dogs at risk for developing canine hip dysplasia. J Am Vet Med Assoc 1997;210:1483–5.
27. Riser WH. The dysplastic hip joint: radiologic and histologic development. Vet Pathol 1975;12:279–305.
28. Smith GK, Gregor TP, Rhodes WH, et al. Coxofemoral joint laxity from distraction radiography and its contemporaneous and prospective correlation with laxity, subjective score, and evidence of degenerative joint disease from conventional hip-extended radiography in dogs. Am J Vet Res 1993;54:1021–42.
29. Evans HE. Miller's anatomy of the dog. 3rd edition. Philadelphia: WB Saunders; 1993. p. 349.
30. Lust G, Bellman WT, Rending VT. A relationship between degree of laxity and synovial fluid volume in coxofemoral joints of dogs predisposed for hip dysplasia. Am J Vet Res 1980;41:55–60.

31. Innes JF. Arthritis. In: Tobias KM, Johnston SA, editors. Veterinary surgery small animal, vol. 1, 1st edition. St Louis (MO): Elsevier; 2012. p. 1078–111.
32. Smith GK, LaFond E, Heyman SJ, et al. Biomechanical characterization of passive laxity of the hip joint in dogs. Am J Vet Res 1997;58:1078–82.
33. Madsen JS, Oxlund H, Svalastoga E, et al. Collagen type III: I composition in hip joints of dogs susceptible to hip dysplasia. J Small Anim Pract 1994;35:625–8.
34. Todhunter RJ, Zaches TA, Gilbert RO, et al. Onset of epiphyseal mineralization and growth plate closure in radiographically normal and dysplastic Labrador retrievers. J Am Vet Med Assoc 1997;210:1458–62.
35. Komsta R, Łojszczyk-Szczepaniak A, Dębiak P. Lumbosacral transitional vertebrae, canine hip dysplasia, and sacroiliac joint degenerative changes on ventrodorsal radiographs of the pelvis in police working German shepherd dogs. Top Companion Anim Med 2015;30:10–5.
36. D'Amico LL, Xie L, Abell LK, et al. Relationships of hip joint volume ratios with degrees of joint laxity and degenerative disease from youth to maturity in a canine population predisposed to hip joint osteoarthritis. Am J Vet Res 2011;72:376–83.
37. Smith GK, Lawler DF, Biery DN, et al. Chronology of hip dysplasia development in a cohort of 48 Labrador retrievers followed for life. Vet Surg 2012;41:20–33.
38. Alexander JW. The pathogenesis of canine hip dysplasia. Vet Clin North Am Small Anim Pract 1992;22:503–11.
39. Gold RM, Gregor TP, Huck JL, et al. Effects of osteoarthritis on radiographic measures of laxity and congruence in hip joints of Labrador Retrievers. J Am Vet Med Assoc 2009;234:1549–54.
40. Steffey MA, Todhunter RJ. Osteoarthritis. In: Bojrab MJ, Monnet E, editors. Mechanisms of disease in small animal surgery. 3rd edition. Jackson (WY): Teton NewMedia; 2010. p. 731–42.
41. Fujita Y, Hara Y, Nezu Y, et al. Direct and indirect markers of cartilage metabolism in synovial fluid obtained from dogs with hip dysplasia and correlation with clinical and radiographic variables. Am J Vet Res 2005;66:2028–33.
42. Chalmers HJ, Dykes NL, Lust G, et al. Assessment of bone mineral density of the femoral head in dogs with early osteoarthritis. Am J Vet Res 2006;67:796–800.
43. Lewis TW, Blott SC, Woolliams JA. Comparative analyses of genetic trends and prospects for selection against hip and elbow dysplasia in 15 UK dog breeds. BMC Genet 2013;14:16.
44. Leighton EA. Genetics of canine hip dysplasia. J Am Vet Med Assoc 1997;210:1474–9.
45. van Hagen M, Ducro B, Broek J. Incidence, risk factors, and heritability estimates of hind limb lameness caused by hip dysplasia in a birth cohort of boxers. Am J Vet Res 2005;66:307–12.
46. Wood JLN, Lakhani KH, Rogers K. Heritability and epidemiology of canine hip-dysplasia score and its components in Labrador retrievers in the United Kingdom. Prev Vet Med 2002;55:95–108.
47. Reed A, Keller G, Vogt D. Effect of dam and sire qualitative hip conformation scores on progeny hip conformation. J Am Vet Med Assoc 2000;217:675–80.
48. Zhang Z, Zhu L, Sandler J, et al. Estimation of heritabilities, genetic correlations, and breeding values of four traits that collectively define hip dysplasia in dogs. Am J Vet Res 2009;70:483–92.
49. Leppänen M, Mäki K, Juga J, et al. Factors affecting hip dysplasia in German shepherd dogs in Finland: efficacy of the current improvement programme. J Small Anim Pract 2000;41:19.

50. Willis MB. A review of the progress in canine hip dysplasia control in Britain. J Am Vet Med Assoc 1997;210:1480–2.
51. Kaneene JB, Mostosky UV, Miller R. Update of a retrospective cohort study of changes in hip joint phenotype of dogs evaluated by the OFA in the United States, 1989–2003. Vet Surg 2009;38:398–405.
52. Hou Y, Wang Y, Lust G, et al. Retrospective analysis for genetic improvement of hip joints of cohort Labrador retrievers in the United States: 1970–2007. PLoS One 2010;5:e9410.
53. Wilson BJ, Nicholas FW, James JW, et al. Genetic correlations among canine hip dysplasia radiographic traits in a cohort of Australian German shepherd dogs, and implications for the design of a more effective genetic control program. PLoS One 2013;8:e78929.
54. Bliss S, Todhunter RJ, Quaas R, et al. Quantitative genetics of traits associated with hip dysplasia in a canine pedigree constructed by mating dysplastic Labrador retrievers with unaffected greyhounds. Am J Vet Res 2002;63:1029–35.
55. Zhu L, Zhang Z, Friedenberg S, et al. The long (and winding) road to gene discovery for canine hip dysplasia. Vet J 2009;181:97–110.
56. Verhoeven G, Fortrie R, van Ryssen B, et al. Worldwide screening for canine hip dysplasia: where are we now? Vet Surg 2012;41:10–9.
57. Marschall Y, Distl O. Mapping quantitative trait loci for canine hip dysplasia in German shepherd dogs. Mamm Genome 2007;18:861–70.
58. Todhunter RJ, Mateescu R, Lust G, et al. Quantitative trait loci for hip dysplasia in a cross-breed canine pedigree. Mamm Genome 2005;16:720–30.
59. Phavaphutanon J, Mateescu RG, Tsai KL, et al. Evaluation of quantitative trait loci for hip dysplasia in Labrador retrievers. Am J Vet Res 2009;70:1094–101.
60. Chase K, Lawler DF, Carrier DR, et al. Genetic regulation of osteoarthritis: a QTL regulating cranial and caudal acetabular osteophyte formation in the hip joint of the dog (Canis familiaris). Am J Med Genet A 2005;135:334–5.
61. Friedenberg SG, Zhu L, Zhang Z, et al. Evaluation of a fibrillin 2 gene haplotype associated with hip dysplasia and incipient osteoarthritis in dogs. Am J Vet Res 2011;72:530–40.
62. Sánchez-Molano E, Woolliams JA, Pong-Wong R, et al. Quantitative trait loci mapping for canine hip dysplasia and its related traits in UK Labrador retrievers. BMC Genomics 2014;15:833.
63. Guo G, Zhou Z, Wang Y, et al. Canine hip dysplasia is predictable by genotyping. Osteoarthritis Cartilage 2011;19:420–9.
64. Bartolomé N, Segarra S, Artieda M, et al. A genetic predictive model for canine hip dysplasia: Integration of Genome Wide Association Study (GWAS) and candidate gene approaches. PLoS One 2015;10:e0122558.
65. Kealy RD, Olsson SE, Monti KL, et al. Effects of limited food consumption on the incidence of hip dysplasia in growing dogs. J Am Vet Med Assoc 1992;201:857–63.
66. Kealy RD, Lawler DF, Ballam JM, et al. Five-year longitudinal study on limited food consumption and development of osteoarthritis in coxofemoral joints of dogs. J Am Vet Med Assoc 1997;210:222–5.
67. Kealy RD, Lawler DF, Ballam JM, et al. Evaluation of the effect of limited food consumption on radiographic evidence of osteoarthritis in dogs. J Am Vet Med Assoc 2000;217:1678–80.
68. Krontveit RI, Nødtvedt A, Sævik BK, et al. A prospective study on canine hip dysplasia and growth in a cohort of four large breeds in Norway (1998–2001). Prev Vet Med 2010;97:252–63.

69. Lopez MJ, Quinn MM, Markel MD. Associations between canine juvenile weight gain and coxofemoral joint laxity at 16 weeks of age. Vet Surg 2006;35:214–8.
70. Madsen JS, Reimann I, Svalastoga E. Delayed ossification of the femoral head in dogs with hip dysplasia. J Small Anim Pract 1991;32:351.
71. Kealy RD, Lawler DF, Monti KL, et al. Effects of dietary electrolyte balance on subluxation of the femoral head in growing dogs. Am J Vet Res 1993;54:555–62.
72. Riser WH, Shirer JF. Correlation between canine hip dysplasia and pelvic muscle mass: a study of 95 dogs. Am J Vet Res 1967;28:769–77.
73. Steinetz BG, Goldsmith LT, Lust G. Plasma relaxin levels in pregnant and lactating dogs. Biol Reprod 1987;37:719.
74. Lust G, Williams AJ, Burton-Wurster N, et al. Effects of intramuscular administration of glycosaminoglycan polysulfates on signs of incipient hip dysplasia in growing pups. Am J Vet Res 1992;53:1836–43.
75. Rettenmaier JL, Keller GG, Lattimer JC, et al. Prevalence of canine hip dysplasia in a veterinary teaching hospital population. Vet Radiol Ultrasound 2002;43:313–8.
76. Witsberger TH, Villamil JA, Schultz LG, et al. Prevalence of and risk factors for hip dysplasia and cranial cruciate ligament deficiency in dogs. J Am Vet Med Assoc 2008;232:1818–24.
77. Paster ER, LaFond E, Biery DN, et al. Estimates of prevalence of hip dysplasia in golden retrievers and rottweilers and the influence of bias on published prevalence figures. J Am Vet Med Assoc 2005;226:387–92.
78. Powers MY, Karbe GT, Gregor TP, et al. Evaluation of the relationship between Orthopedic Foundation for Animals' hip joint scores and PennHIP distraction index values in dogs. J Am Vet Med Assoc 2010;237:532–41.
79. LaFond E, Breur GJ, Austin CC. Breed susceptibility for developmental orthopedic diseases in dogs. J Am Anim Hosp Assoc 2002;38:467–77.