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LATEST DATA TO THE GENETICS OF CANINE HIP DYSPLASIA

A REVIEW OF LITERATURE

DIPLOMA WORK

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1. INTRODUCTION

Canine hip dysplasia is a developmental orthopaedic disorder and was first described by Schnelle in 1935 (35). Hip dysplasia is a polygenic and polyfactorial disorder characterized by instability of the coxofemoral joint leading to secondary degenerative joint disease. Secondary changes are caused by abnormal wearing of the bone surfaces, and can result in acetabular bone sclerosis, osteophytosis, thickened femoral neck, capsule fibrosis and subluxation or luxation of the femoral head. The resulting osteoarthritis is irreversible, thus the only way to improve the welfare of susceptible breeds is through genetic selection. Many studies have confirmed that hip dysplasia has a polygenetic hereditary aetiology, conditioned by environmental factors. Amount of physical exercise, weight gain, growth rate, breed and nutrition are some factors that will influence the expression of the disease.

The aim of this literature review is to highlight the characteristics and latest research within this field. I will discuss the genetic background, breed predisposition and clinical appearance. I will also discuss the diagnosis, treatment and prevention. In addition to this I will also discuss the work of the Norwegian Kennel Club. The hip screening program organized by the Norwegian Kennel Club implies standardized evaluation and recording of radiographic hip status, and the grading is done according to the protocol of the Fédération Cynologique Internationale (FCI).

2. LITERATURE REVIEW

2.1. Anatomy

The coxofemoral joint is a spheroidal joint composed of the head of the femur (caput femoris) and the acetabulum.

The acetabulum is a deep cotyloid cavity to which all three pelvic bones contribute. In carnivores, an additional fourth bone in the centre of the cavity is present. This is the small acetabular bone (os acetabuli). Craniolaterally the acetabulum is composed of the body of the ilium, the body of the ischium caudolaterally and the body of the pubis medially. The cavity of the acetabulum is comprised of the articular lunate surface (facies lunata) and the non-articular acetabular fossa (fossa acetabuli). Facies lunata is shaped like a halfmoon and indented medially by the deep acetabular notch (incisura acetabuli). The articular surface is enlarged by a fibrocartilagenous articular lip (labrum acetabulare). The articular lip is attached to the acetabular rim and the joint capsule. (19)

The femur can be into three basic segments: proximal extremity, shaft, and distal extremity. The proximal extremity consists of the head and is curved medially. It has a hemispherical shape and is interrupted by a circular notch in the centre, the fovea capitis. The head of the femur is separated from the shaft by a distinct neck (column ossis femoris). Between the neck of the femur and the greater trochanter (trochanter major) the trochanteric fossa is located. This is where the deep muscles of the hip inserts. (20)

The ligament of the head of the femur (ligamentum capitis ossis femoris) makes a notch in the joint capsule. This ligament extends from the fovea in the head of the femur to the acetabular fossa, and is covered with synovial membrane. The other ligament of the hip joint is the transverse acetabular ligament (ligamentum transversum acetabuli). It forms a bridge over the acetabular notch and keeps the other ligament in its place.

The muscles of the hip includes: rump muscles, caudal muscles of the thigh, medial muscles of the thigh and inner pelvic muscles. (21)

2.2. Pathogenesis

Canine hip dysplasia is a polyfactorial developmental disorder, mostly occurring in large dog breeds. The disease is characterized by laxity and incongruency of the joint causing an uneven distribution of the forces eventually leading to degenerative joint disease. The occurrence is affected by nutrition, growth rate, exercise and hereditary factors. The pathophysiological basis is the disparity between the hip joint muscle mass and a rapid bone development (17). Since the joint capsule and the conformation of the joint are major contributors to the stability an abnormality in the capsule may cause laxity (36). In canine hip dysplasia the formation of a normal functioning contact between the acetabulum and the head of the femur fails to occur. Puppies that carry a genetic predisposition to the disease will mainly have normal hips at birth, and the changes in the joint can start as early as the first weeks of life. In young dysplastic dogs there may or may not be osteoarthritis present, but synovitis is and this will cause a thickening of the joint capsule. There can also be an injury of the articular cartilage which will progress to cartilage degeneration and deformation of the bone. As a response to the inflammation and instability of the joint the bone will start to remodel. Finally the capsule will thicken with chronic fibrosis and the laxity will decrease (36).

Subluxation of the femoral head will reduce the contact area between the femoral head and the acetabulum to an area between 10 o'clock and 2 o'clock. This will lead to a build-up of stress in the area, leading to overload of the acetabular rim, the tissue loose its elasticity and contour, and microfactures occur (2). The microfractures occurring along the acetabular rim are most likely the cause of pain in dogs aged 5 to 8 months. These fractures heal and some remodeling occurs by 11 to 13 months (1). The hip will then become more stable and pain is decreased markedly (2).

Since the weight-bearing becomes abnormal there can also be changes occurring in the angles of the femoral neck and the acetabular inclination angles (1).

2.3. Clinical appearance

Appearance of clinical findings vary with the age of the animal, and there are two recognizable groups: Young dogs between age 4 and 12 months, and older animals (over 15 months age) with chronic disease (2)

The clinical appearance of the canine hip dysplasia depends on the severity of the dysplasia, as well as the degree of the degenerative joint disease. The signs of lameness will be more obvious after minor trauma and exercise (36). Clinical signs of joint laxity can be observed in puppies as early as 3 months age (30).

Typical signs of a dog with hip dysplasia (36):

- Reduced activity, less running and jumping.
- Problems with walking in stairs, laying down and standing up.
- Reduced range of motion.
- Pain upon extension and flexion of the hindlimbs.
- The owner of veterinarian may hear a faint sound of popping coming from the hip. Crepitation may also be heard.

The severity of the clinical signs may not always correlate with the radiographic findings, and the lameness may be mild, moderate or severe. The owner may describe the dog as "lazy" as the animal lies down after play, and possess difficulties standing up and lying down. Another typical sign of hip dysplasia is the characteristic "bunny hopping" (17).

In young growing animals there may be underdeveloped muscles of the hindlimb, whereas in older animals the muscles may be atrophied. The clinical signs may be more severe in middle-aged and older dogs (30).

A positive Ortolani sign will occur in most animals affected with hip dysplasia. This is a snapping sound occurring when the femoral slips in and out of the acetabulum when adduction and proximal pressure is applied to the femur followed by abduction of the limb. (2).

2.4. Diagnosis

The hip joint laxity can be estimated with the Barlow maneuver and the Ortolani test. To perform the Ortolani test the dog is placed in a lateral or dorsal recumbency. The starting position is when the stifle is flexed and the hip joint is in a neutral position. The limb should then be moved axially and then slowly abducted. A snapping sound can be felt and sometimes heard is the point at which the head of the femur snaps back into the acetabulum. The point at which this snapping is felt should be noted and the angle measured. The snapping is referred to as a positive Ortolani sign. The limb should then be adducted slowly towards the neutral position. When the femoral head again subluxates should be measured and is referred to as the angle of luxation (1). As these tests are subjective they can give both false positive and false negative results. In addition, these tests should be done under general anaesthesia, as a negative Ortolani test in an awake tense animal should be considered unreliable. It also relies on the skills of the examiner (36).
Palpation for joint laxity in older animals is usually without results, due to the fibrosis of the joint capsule and the shallow acetabulum (2).
For an objective evaluation of the changes in the hips in a dog with hip dysplasia is by radiographic examination. The presence and stage of the level of arthrosis can be evaluated, as well as the anatomical structures and their relationship to each other (30).

The FCI (Fédération Cynologique Internationale) have made a procedure regarding the positioning of dogs for radiographic evaluation of hip dysplasia (7). There are two positions possible and for both positions the dog should be sedated to ensure a complete relaxation of the muscles. The dog shall be placed in a cradle to ensure a correct ventrodorsal position and the left or right side is marked with a lead marker. It is important that the beam is collimated so the final picture will show the entire pelvis and both patellae.
Position 1 (official position) involves extended hind limbs. The hind limbs are held at the tarsi, the stifles are adducted and the entire limbs are pronated. Then the limbs are extended and pushed down against the table top. To ensure a proper position of the femora the paws are pulled inwards. If the positioning is correct the radiograph will show the entire pelvis

with both wings of the ilium and the obturator foramens are of equal size and the sacroiliac joints appear similar. The femurs are parallel to each other and parallel to the spinal column. The patellae are superimposed over the midline of the femur, projected between the two fabellae. In addition the lead marker should be clearly visible.
Position 2 (additional position) involves abducted hind limbs. The femurs should be abducted and in an average sized dog (e.g. retrievers) the distance between the tarsi and the table should be 30-40cm. The beam shall be centered over the hip joints and collimated to ensure a complete visualization of the pelvis. If the position is correct the radiograph will show that the entire pelvis visible and symmetrical, the last lumbar vertebra is seen, the greater trochanter is caudally projected and the cranial border of the femoral head-neck intersection is positioned outside the acetabulum.

The FCI have classified the severity of Hip Dysplasia into 5 different grades: A, B, C, D and E (8).

A. Normal hips. No signs of hip dysplasia.
    a. The femoral head and the acetabulum are congruent.
    b. The joint space is narrow and even.
    c. The craniolateral rim appears sharp and slightly rounded.
    d. The acetabular angle according to Nordberg is about 105 degrees.
B. Transitional. Near normal hip joints.
    a. The femoral head and the acetabulum are slightly incongruent.
    b. The acetabular angle according to Nordberg is about 105 degrees.
    c. The femoral head and the acetabulum are congruent.
    d. The centre of the femoral head lies medial to (or on) the dorsal rim of the acetabulum.
C. Light. Mild hip dysplasia.
    a. The femoral head and the acetabulum are incongruent.
    b. The acetabular angle according to Nordberg is about 100 degrees and/or there is a slightly flattened craniolateral rim.
    c. No more than slight signs of osteoarthrotic changes, meaning slight osteophytes, on the femoral head and neck. (Subchondral sclerosis along the acetabular margin without other signs of mild dysplasia is not enough).
D. Medium. Moderate hip dysplasia.

a. Obvious incongruency between the femoral head and the acetabulum with subluxation.
b. Flattening of the craniolateral rim and/or osteoarthrotic signs.

E. Severe hip dysplasia.
   a. Obvious changes of the hip joints, such as luxation or distinct subluxation.
   b. Deformation of the femoral head and acetabulum (mushroom shaped, flattening) and other signs of osteoarthrosis.

According to the FCI scale, hips with grade C, D and E are considered with dysplastic changes (38). One method used for evaluating the radiographs includes six anatomical structures of the hip joint that represents six radiographic parameters. The presence and severity of canine hip dysplasia can be evaluated based on these six parameters. Depending on the severity of the pathological changes, grades from 0 to 5 have been given to each of the parameters (10).

Table 1: Radiographic criteria for grading canine hip dysplasia (10).

Score	0	1	2	3	4	5
Nordberg angle (JS = joint space)	> or = 105 degrees	> or = 105 degrees with slightly widened JS. Or <105 degrees and narrow JS.	> or = 100 degrees	> or = 90 degrees	> or = 80 degrees	< 80 degrees
Relation femoral head centre (FHC) and dorsal acetabular edge (DAE)	FHC medial to DAE (>2mm). Narrow JS	FHC medial to DAE (1,2 mm) and minimally divergent JS.	FHC super-imposed on DAE. JS is slightly divergent.	FHC lateral to DAE (1-5 mm). JS is moderate divergent.	FHC lateral to DAE (6-10 mm). JS is markedly divergent.	FHC lateral to DAE (>10mm or luxation)
Craniolateral acetabular edge (CAE)	Parallel to femoral head.	Horizontal on lateral ¼.	Slightly flattened or mild exostosis.	Moderate flattened, mild exostosis.	Markedly flattened, moderate exostosis.	DAE absent, acetabulum markedly deformed.
Cranial subchondral acetabular bone	Fine and even.	Even.	Slightly thickened laterally, slightly reduced medially.	Moderately thickened laterally, moderately reduced medially.	Markedly thickened laterally, may not be present medially.	Blending with lateral pelvic rim or absent.
Femoral head (H) and femoral neck (N).	H: round and smooth. N: well demarcated.	H: round N: poorly demarcated	H: slightly flattened. N: mild exostosis.	H: moderately flattened. N: mild exostoses.	H: moderate flattened. N: moderate exostoses	H: Severely deformed. N: Massive exostoses.
Morgan-line	Not visible	Edged shoulder on flexed limb view.	Fine linear spur (up to 1mm wide).	Well defined spur (up to 3mm wide).	Broad and irregular spur (>3mm wide).	Spur incorporated in or superimposed by general exostoses.

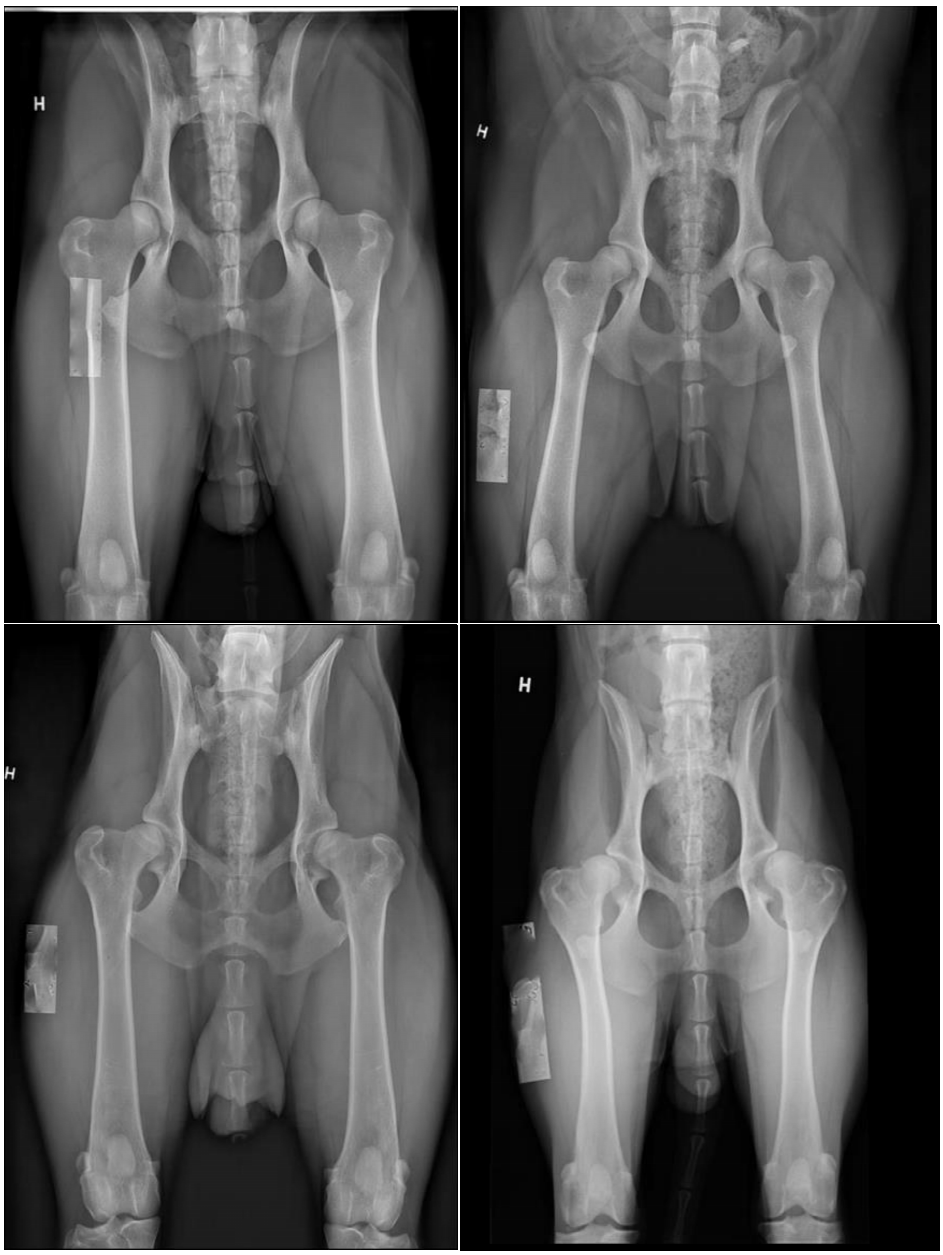

Figure 1. Radiographs of hip joints graded as free (top left), mild (top right), moderate (bottom left), and severe (bottom right) hip dysplasia (pictures provided by Hege K. Skogmo).

2.5. Treatment and management

Regarding canine hip dysplasia many factors influence the choice of treatment. Age, history, clinical signs and the results obtained from physical and radiological examinations are important factors to consider. In addition the owner's expectation and personal economy play a key role. Surgical interventions are expensive in Norway, and if the owner doesn't have insurance or a personal economy to support the economic load the treatment of choice often narrows down to conservative therapy.

Most of the dogs affected by hip dysplasia respond well to conservative therapy. This will include reduction of body weight if the animal is obese; prevent obesity if the animal is of normal body condition score, and anti-inflammatory drugs (36). Activity should be minimized to restrict exercise below a threshold level at which the hips can tolerate without producing pain and fatigue (2). Dogs that have developed degenerative joint disease (DJD) should avoid high-impact exercise such as running and jumping. Low-impact exercise is encouraged, and include for example swimming and walking on a leash (31).

The age of the dog influences the conservative treatment also. In young dogs and puppies which haven't developed osteoarthritis yet, the effect of nutrition plays a key role. Food restriction during growth will cause the dog to reach mature body size a bit later, but in addition the muscles and skeleton will grow in congruence. A study made by Hedhammar in 1974 (14) showed the influence of overfeeding Great Dane puppies. Compared to puppies that were not overfed the puppies with ad libitum feeding showed an increased incidence in skeletal disorders. These skeletal disorders included the canine hip dysplasia. Another study made by Hazewinkel *et al* in 1986 (13) showed that the intake in excess calcium in growing dogs may cause developmental disorders of the skeleton. The reason of this was shown to be that growing puppies cannot down-regulate the intestinal absorption of calcium, thus resulting in toxic effects of the excess calcium.
Older dogs may already suffer from osteoarthritis, and exercise modification, weight control and analgesic treatment is central in managing the disease (36). Feeding commercial "joint diets" containing supplements can decrease the pain and inflammation caused by the DJD. These supplementations include omega-3 polyunsaturated fatty acids (PUFAs),

eicosapentaenoic acid (EPA) and antioxidants (vitamin E, vitamin C, beta-carotene, zinc and selenium) (31).

Pharmacological therapy includes non-steroidal anti-inflammatory drugs (NSAIDs) due to their anti-inflammatory and analgesic effects. As the primary action of most NSAIDs is the inhibition of cyclooxygenase, the synthesis of prostaglandins will be prevented. Prostaglandins are responsible for pain and inflammation, and thus the NSAIDs will reduce pain and inhibit the release of inflammatory mediators. Due to the side-effects of NSAIDs, the owners should be instructed to look for gastrointestinal symptoms, such as melena, vomiting and inappetence. The two most commonly used NSAIDS in Norway are Metcam (meloxicam) and Rimadyl (carprofen). The dosage for Metacam is 0,2mg/kg PO once, and then 0,1mg/kg PO once a day. The dosage for Rimadyl is 2,2 mg/kg PO twice a day. Chondroprotective agents can also be administered to improve the cartilage biosynthetic activity, decrease the synovial inflammation and inhibit degradative enzymes in the joint. Glucosamine and chondroitin sulfate are two examples of this, and they can be administered together or separately. Other disease-modifying chondroprotective agents are pentosan polysulphate (with the drug name Pentosan 100) and polysulfated glycosaminoglycans (with the drug name Adequan). It is important to note that to achieve the maximum effect from all these products they should be administered before the DJD has occurred (31).

Other nonsurgical methods of management include acupuncture, mesenchymal stem cell therapy, hydrotherapy and extracorporal shock wave therapy (18).

Surgical therapy may be a treatment of options in patients with clinical signs. Surgical options include total hip replacement, pelvic osteotomy, juvenile pubic symphysiodesis, and femoral head and neck excision (11).
Juvenile pubic symphysiodesis is performed in puppies under 20 weeks age, and will alter the growth of the pelvis and the degree of the ventroversion of the acetabulum. Under general anaesthesia the dog is positioned in dorsal recumbency. By using a spatula electrode set at 40 watts, ablation is performed by placing the electrode against the symphysis for about 10 seconds. Repeat it every 2-3 mm along the symphysis (5).
Pelvic osteotomy is performed in young dogs and indicated in patients with an athletic life. It is useful in its way that it axially rotate and lateralize the acetabulum to increase the dorsal

coverage of the femoral head. During pelvic osteotomy the patient is in lateral recumbency, and a canine pelvic osteotomy plate is recommended. 20-30 degrees of acetabular rotation will give the maximum increase in the articular coverage of the hip. The use of 9 hole TPO plates or double plating may limit the risk of losing the implants in larger breeds (9).
Total hip replacement is a highly advanced procedure and is considered a salvage procedure for hip joints that cannot be repaired. Thus the joint is removed and replaced. THR should be done as late in life as possible, and should be delayed until a correct body condition is obtained (11).
Femoral head and neck excision is a method used when conservative management has failed, or when financial or medical constrains exclude other surgical options. The excision will limit the bony contact between the femoral head and the acetabulum and allows a formation of a fibrous false joint. Since this will cause an unstable joint the clinical function postoperatively is unpredictable (11).

In a study from the Ankara University, pre- and postoperative clinical and radiological outcomes in dogs with hip dysplasia was evaluated after performing juvenile pubic symphysiodesis. 10 dogs at an age of 3 to 5 months with hip dysplasia were examined before the surgery and 1, 3 and 6 months after the surgery. Pain scoring of hip extension, Barden signs and Ortolani signs were examined in addition to measurement of the Nordberg angles on standard ventrodorsal radiological examination. After the procedure the study showed that the acetabulum fully covered the femoral head as a result of a ventrolateral rotation of the acetabulm. The Ortolani sign, Barden sign and hip extension test all turned from positive to negative. The researchers at the Ankara university concluded that the juvenile pubic symphysiodesis is a safe and successful procedure for large breed puppies aged 3-5 months that are predisposed to hip dysplasia or showing initial clinical signs (34).

The prognosis for a dog diagnosed with hip dysplasia is highly variable and the environment and health of the animal plays an important role. Surgery is beneficial if it is indicated and performed with precision, but an alteration in lifestyle is required in dogs where surgery isn’t performed (17).

2.6. Breed predisposition

Hip dysplasia is a condition that can affect all dog breeds, including mixed breeds. It is however mostly seen in large sized dogs (43). Many studies have confirmed that hip dysplasia has a polygenetic hereditary etiology, conditioned by environmental factors, and that the heritability is assessed in a range of 0,1 to 0,6 in populations of different dog breeds. Dysplastic dogs have a higher risk of getting offspring with hip dysplasia, but the frequency of hip dysplasia is smaller in offspring of parents with certified good hips (grade A or B). The incidence of the disease is higher in dogs with parents that don't have certified hips (40).

The occurrence of canine hip dysplasia in different breeds varies from country to country. This is due to the fact that there are differences in the popularity of individual breeds in various countries, as well as differences in the success of the control programs.

In a study from 2011 made at the University of Zagreb (38) 5381 dogs of 137 different breeds were tested for hip dysplasia. 18,75% of the tested dogs was diagnosed with dysplasia (grade C, D or E), but the frequency varied between the different breeds. The most frequent breed diagnosed with hip dysplasia was English Bulldog (81,33%), while the Rhodesian Rigdeback was the breed with the lowest frequency (3,33%) (**Table 2**).

A study made at the Helsinki University in Finland showed that the existence of a major gene responsible for hip dysplasia was considered likely in four breeds studied. These four breeds were the German Sheperd, the Golden Retriever, the Labrador Retriever and the Rottweiller (28).

Table 2 shows the most frequent breeds examined and the occurrence of dysplasia.

Breed	No. of examined dogs	Male/Female	No. of dogs with HD (%)	Male/Female (with dysplasia)
Labrador Retriever	665	225/440	110 (16,54)	41/69
Golden Retriever	488	192/296	111 (22,7)	47/64
Rottweiler	455	175/280	51 (11,21)	26/25
Croatian Mountain Dog	410	177/233	118 (28,78)	54/64
American Staffordshire Terrier	398	173/225	81 (20,36)	36/45
Belgian Shepherd dog	290	141/149	11 (3,72)	8/3
Doberman	233	86/147	9 (3,86)	2/7
German boxer	202	60/142	45 (22,25)	14/31
Yugoslavian Shepherd dog	163	62/101	67 (41,10)	21/46
Great Dane	119	47/72	19 (15,97)	9/10
Bernese Mountain dog	110	29/81	15 (13,64)	2/13
Dogue de Bordeaux	102	40/62	40 (39,22)	14/26
German short-haired Pointing dog	100	46/54	3 (30,00)	0/3
English bulldog	75	37/38	61 (81,33)	33/28
Dogo Argentino	79	28/51	36 (45,57)	12/24
Border Collie	65	29/36	6 (9,23)	4/2
Samoyed	64	21/43	8 (12,50)	3/5
Rhodesian Ridgeback	62	31/31	2 (3,33)	2/0
Bullmastiff	51	21/30	26 (50,98)	8/18
Caucasian Shepherd dog	51	22/29	22 (43,13)	10/12

2.7. Genetic background

Canine hip dysplasia are hereditary malformations that develop during a period of rapid growth, and have been reported as quantitative traits occurring in several breeds (23, 40). In addition to quantitative inheritance, the possibility of a major gene (42) has been suggested. The first hypotheses on the mode of inheritance of canine hip dysplasia were simple monogenic models, either for recessive (12) or dominant transmission (37). A study made by Chase *et al.* in 2004 (4) in Portuguese water dogs determined two quantitative trait loci on canine chromosome 1 that are linked to laxity in the hip joints as defined by the Nordberg angle. Another quantitative trait loci on canine chromosome 3 was significantly linked to acetabular osteophyte formation in the hip joints of Portuguese water dogs (3).

A study made in in Finland in 2002 (27) examined the mode of inheritance of hip and elbow dysplasia in 4 breeds: the Labrador Retriever, the German Shepherd, the Golden Retriever and the Rottweiler. For the time being, the presence of segregating major genes was assessed based on the frequency of dysplasia occurring in offspring of individual sires. The study did not reveal any signs of major genes, but it does not, however, rule out the possibility of such a gene affecting the trait for hip dysplasia. In a study like this, the effects of a major gene have to be very large to influence the distributions of the trait.

Another study made in Finland in 2004 (28) aimed to assess the probable existence of a major gene causing hip and elbow dysplasia. Also this study included four breeds: the Golden Retriever, the Labrador Retriever, the German Shepherd and the Rottweiler. 34 140 dogs were included in the study, and the pedigree information and official radiographic examination was obtained from the Finnish Kennel Club. Each dog was given a separate grade for the left and right hip, and the average of these two grades was used as the trait studied. The data was obtained from the period between 1988 and 2000.
The data was analyzed by a polygenic and a mixed inheritance model. In the polygenic models, fixed and random environmental effects and additional genetic effects were included. When adding the effect of a major gene to the polygenic models, the mixed inheritance model was made. The major gene was modeled as an autosomal biallelic locus with the probability for transmission according to Mendelian inheritance laws. In all the four

breeds included in the study, the probability of a major gene was likely for hip dysplasia. The study concluded that a considerable genetic progress could be made possible by selection against these major genes. To acquire more reliable information about the existence of the possible major genes would require further study.

In a study made by Todhunter *et al* in 1999 the two major genes reported to affect hip dysplasia in the Labrador Retriever and Greyhound crosses were dominant (42). In that study, the hip dysplasia phenotypes were divided into different components, such as joint laxity and dorsolateral subluxation. 147 dogs representing 4 generations were participated in the study, and 96% of the alleles showed inheritance according to Mendel's laws. By using microsatellite markers distributed in 38 autosomes and the X chromosome, several quantitative trait loci was found. On four chromosomes, QLT for at least two phenotypes was identified. On eight chromosomes, QLT was identified for one phenotype. They found that the main challenge with mapping qualitative traits was not the detection of the QLT, but finding the genes that lie under them.

A study made at the University of Veterinary Medicine in Hannover (16) also aimed at clarifying the mode of inheritance of canine hip dysplasia. Complex segregation analyses were carried out in 8567 German Shepherd dogs from 20 families with three to four generations. In addition to polygenic gene effects, the existence of a major gene was detected. The study made in Hannover a mixed model with a dominant major gene effect was used for dichotomous encoding. The animals were divided into two groups: Animals without signs of hip dysplasia, and animals with borderline/slight to severe hip dysplasia. In addition, a mixed major gene inheritance was shown for a binary trait where the dogs falling into the borderline category was assigned to the category free from hip dysplasia. For a trichotomously encoding, the animals were divided into three groups: Without signs of hip dysplasia, borderline hip dysplasia, and mild to severe hip dysplasia. For the unfavorable homozygote genotype AA was found only in small frequencies, but the probability for the genotype AB was high in animals affected by HD. The study concluded that to improve the breeding programs in German shepherd dogs the frequency of the allele A should be reduced. Both the dichotomous and the trichotomous encoding for the trait for canine hip dysplasia confirmed the presence of a major gene effect. This is in agreement with other published studies on this disease (23, 28).

2.8 Prevention

Canine hip dysplasia is a polyfactorial skeletal disorder. It is a common disorder in large breed dogs and represents a great concern regarding the welfare of the animal. Official screening for hip dysplasia and selective breeding have been used for decades, and there are many different theories on how to influence the progression of hip dysplasia. Body weight and body condition, nutrition and exercise all play important roles in the development of degenerative joint disease, although it will not eliminate the hip dysplasia (36).

A study made at the Norwegian School of Veterinary Science showed the risk of housing and exercise associated with the development of hip dysplasia in Labrador Retrievers, Leonbergers, Newfoundlands and Irish Wolfhounds in Norway. 501 client-owned dogs from 103 separate litters were assessed from birth till official radiographic screening age. For Labrador Retrievers and Irish Wolfhound this age is 12 months, while for Newfoundlands and Leonbergers the official screening age is 18 months. The owners were given questionnaires for the information regarding housing and exercise before and after weaning. The results showed that puppies walking in stairs from birth till age 3 months had an increased risk of developing hip dysplasia. Factors that decreased the risk of developing the disease were birth during spring and summer, exercise without leash and being born on a farm. As a result of this study the owners of these breeds should be recommended to avoid puppies under 3 months age walking in stairs. In addition they should be recommended that the puppies are allowed outdoor exercise on soft ground in moderately rough terrain (22).

Many recommendations regarding environment and housing of puppies and young dogs can be made, but the most significant prevention is through selective breeding. The breeding of two dogs with excellent hips (grade A or B) cannot guarantee that all the offspring will be free from the disease (36). The osteoarthritis that can develop in a dog with hip dysplasia is irreversible and thus the only way to achieve a long lasting improvement in the welfare of dogs is by selective breeding (26). Despite the presence of evaluation schemes worldwide, the accompanying breeding guidelines have elicited only a weak selection (25, 39). The polygenetic background of the hip dysplasia is the main reason why the reduction in the incidence of this disease is slow (23). If owners only insisted on purchasing puppies that

have parent and grandparents with certified hips of grade A or B, then the majority of the problem will be eliminated. It is also the breeder's responsibility, and they should only breed two dogs with excellent or good hip status which have parents with the same hip status. For the best results the buyers should look at the hip status from 3-4 generations prior to the puppy (36).

The role of nutrition plays an important role in the frequency and severity of the disease. Overfeeding rapidly growing puppies of large or giant breeds will not itself cause hip dysplasia, but maximize the expression in genetically predisposed animals. Dogs on restricted diets have significantly decreased osteoarthritis in their hips and other joints. On the other hand, dogs that are fed on a restricted diet and thus masking their phenotypic expression of the disease, may pass the susceptibility genes to their progenies (36).

In North America, selection methods to improve the genetic composition of dog breeds regarding hip dysplasia have been based on radiographic hip joint screening, semiopen (Orthopedic Foundation for Animals) and closed (PennHIP) hip joint registries, as well as organized breeding programs (33, 44, 45). Through these breeding programs the prevalence of HD has decreased. For example, the prevalence of hip dysplasia in German Shepherds at age 12 to 16 months has decreased from 55% to 24% after 5 generations of selection (40), and in Labrador Retrievers it decreased from 30% to 10% (23, 24).

A study made by Malm *et al* (29) aimed at the evaluation of two selection strategies for the improvement of the hip status in dogs: Selection based on phenotypic records, and the best linear unbiased prediction (BLUP). Furthermore, optimum contribution selection (OCS) was considered. Two traits were evaluated: the hip dysplasia as a categorical trait, and a continuous trait intended to represent the other characteristics of the breeding goal. Hip dysplasia as a continuous trait gave a better genetic gain compared to hip dysplasia as a categorical trait. BLUP uses information from relatives to predict the outcome on the offsprings, and in all scenarios BLUP gave a larger genetic gain than selection based on phenotype. On the other hand, BLUP selection resulted in a higher incidence of inbreeding, and thus OCS was applied. In this way the rate of inbreeding was lowered to the same level as for selection based on phenotype, but with an increased improvement of the genetics.

3. THE WORK OF THE NORWEGIAN KENNEL CLUB (NKC)

3.1. The Kennel Club's breeding strategy

The Norwegian Kennel Club's breeding strategy (41) is based on ethical principles for breeding and was admitted in November 2007 and revised in October 2012. The kennel club's main target is to achieve functionally healthy dogs with anatomy and mentality that is typical for the breed, and can live a long and healthy life. For NKC it important that when choosing animals for breeding, the individual dog as well as the breed shall be evaluated. It is not enough to only consider the results of screening tests, such as radiographic screening for hip dysplasia, or DNA-testing.

The members of the Norwegian Kennel Club are obliged to comply to the NKC's ethical ground principles for breeding, the FCI's code of breeding ethics, as well as breeding according to the strategy set by the NKC.

Central points in the breeding strategy especially relating to hip dysplasia:

- Only functional and clinically healthy dogs should be used in breeding. If close relatives of a dog with known or assumed heritable disease is to be used in breeding, it should be bred with a dog with a family history of no or low incidence of that disease.
- Inbreeding should be avoided.
- Screening of certain diseases should be recommended for breeds in which the disease has an impact on the functional health and welfare of the animal.
- Raising puppies with special attention to nutrition, exercise and social stimuli, is an important foundation in achieving a good physical and mental health.

3.2. The NKK's hip dysplasia program

The radiographic screening for hip dysplasia has been going on worldwide since the beginning of the 1970's. The FCI established procedures and requirements for official screening, and the first Norwegian veterinarian that became an official image reader was Petter Heim in 1972. In the beginning the identification marking of a dog was voluntary, but later this was made obligatory. From the beginning of the 1990's the microchip made the identification a lot easier and safer. The first breeds where a known HD status was required for the parent animals of puppies that were going to be registered was Rottweilers, German Shepherds, Newfoundlands and St.Bernhards (from 1987). Later other breed clubs followed, including Irish setters, Gordon setters, English setters, Retrievers, Breton and several others. From 2005 progenies after dogs with diagnosed hip dysplasia was registered with a prohibition to be further bred.

The FCI has designed procedures for imaging and reading of hip dysplasia screening, from which the Norwegian Kennel Club has adopted and use in their HD program (15). At NKC there is two veterinarians that study and grade about 9000 radiological images each year. The FCI requirements that the Norwegian Kennel Club has adopted concern administration, identification and procedure of the screening, as well as the procedure for a prospective appeal (6).

First of all, the dog has to have reached a minimum age before the radiographic imaging takes place. For most breeds this age is 12 months, but for large and giant breeds the minimum age is 18 months. These breeds are Bullmastiff, Bordeaux dogge, Great Dane, Leonberger, English mastiff, Napolitan mastiff, Newfoundlands, Landseer, Saint Bernard and Pyrenean mountain dog. The dog needs to be identified by microchip.

The date, time, place and responsible veterinarian has to be stated, in addition to information about the owner. The dog's name, registration number, birth date, sex and breed also need to be confirmed. The registration number and the birth date is the ones stated on the pedigree. The owner must sign the form to confirm that above information is correct and that they are known with the requirements for official hip dysplasia screening. The veterinarian should confirm that all the above information is correct and that the microchip was checked. In addition, the veterinarian needs to write down the active substance and dosage used for sedation, and the body weight of the dog.

On the radiograph, the dogs microchip number, the date of when the radiographs were taken and the marks for left or right side needs to be included on the image, and may not be removed prior to evaluation. The veterinarian will send the image directly to NKC and the time needed for interpretation by the NKC's specialized veterinarian is about 10 days (32).

In case of an appeal filed by the owner of a dog, the images need to be interpretated by another veterinarian at NKC. The evaluation of the appeal is based on the initial radiograph and the appeal panel can request that additional radiographs need to be taken. If several radiographs are submitted they shall be evaluated with equal importance, and the decision of the appeal procedure is final.

4. DISCUSSION

Hip dysplasia is a developmental anomaly in the hips, and can affect one or both joints. The defect presents and incongruent relationship between the acetabulum and the femoral head, and secondary changes will occur in and around the joint.

The development of the disease is due to a combination of environment and heritability. One suspects that a dog will not develop hip dysplasia unless there is a genetic predisposition, but a dog doesn't need to develop the disease even though it is genetically predisposed. This predisposition results from combinations of relatively small quantitative effects on phenotype due to variations within a large number of genes. So far, the selection has mainly been based on the observable phenotype through radiological examination. This selection has been largely ineffective since these are complex traits that are strongly influenced by the environment. Until genetically based tests are available, the radiologic examination of the hips is used for hip dysplasia screening in veterinary clinics.

In the case that a major gene is present in dog populations, why is it then the case that hip dysplasia still is a significant disease occurring in German shepherds when the screening program started over 40 years ago? It is important to keep in mind that several factors, other than the major gene, influence the development of the disease. There is a great possibility that more than one major gene exists, and that these genes at other loci override the dominant major gene effect found in previous studies.

Canine hip dysplasia has been shown to manifest phenotypically more frequently under disadvantageous environmental conditions, such as excessive feeding and a high body weight. If dogs are selected only on the basis of their phenotypical hip status, as a common strategy in many breeds, then genetically predisposed dogs raised under beneficial environmental conditions might not have been detected phenotypically, and can thus pass their undesirable alleles to their offspring. Furthermore, the breeding of dogs with grade B (according to the FCI scale) contributes to the preservation of dominant alleles in the population. There are studies that show that phenotypic selection against HD is more effectively if a clear distinction is made between dogs graded with A or B hip status,

compared to when A and B are lumped together, even though both these grades are considered as normal hips.

There is less information regarding the genotypic correlation between the phenotypes and the impact of hip dysplasia on canine welfare. Although the phenotypes chosen as the basis for these control schemes have displayed heritable phenotypic variation in many studies, success in achieving improvement in the phenotypes have been mixed. There is significant room for improvement in the current schemes, for example through the use of estimated breeding values (EBVs), which can combine a dog's CHD phenotype with CHD phenotypes of relatives, other phenotypes as they are proven to be genetically correlated with CHD (especially elbow dysplasia phenotypes), and information from genetic tests for DNA markers as such tests become available. In addition, breeding clubs should be encouraged and assisted to formulate rational, evidence-based breeding recommendations for canine hip dysplasia. These are some of the improvements that can be made to safely and effectively reduce the impact of canine hip dysplasia.

5. CONCLUSION

Regarding the etiology of canine hip dysplasia many observations have been made. The following are among the most important:

- There is a polygenetic predisposition to congenital dislocation of the hip with ***multiple factors*** that influence and ***modify the disease***. Several studies conclude that there are a ***major gene present*** responsible for the development of the disease.
- ***Environmental factors are superimposed*** on the genetic susceptibility of the individual.
- The biochemical explanation of the disease is that is represents a ***disparity between the primary muscle mass and disproportionally rapid skeletal growth***.
- The hip joints are normal at birth. Failure of muscles to develop and reach functional maturity concurrently with the skeleton results in joint instability. Abnormal development is induced when the acetabulum and femoral head pull apart and initiate a series of changes that end in the recognizable disease of hip dysplasia.
- ***Bony changes*** of hip dysplasia are a result of failure of soft tissue to maintain ***congruity between the articular surfaces of the femoral head and acetabulum***.
- The disease is ***preventable*** if hip joint congruity is maintained until ossification makes the acetabulum less plastic and the surrounding soft tissues becomes sufficiently strong to prevent femoral head subluxation. Under the usual circumstances tissue strength and ossification progress sufficiently to prevent the disease ***by 6 months age***.
- Dogs with greater pelvic muscle mass have more normal hip joints than those with a relatively smaller pelvic muscle mass.
- The onset, severity and incidence of hip dysplasia can be reduced by restricting the growth rate of puppies.

Hip dysplasia is a disease that will develop while the dog grows. A dog that has developed HD may experience problems of varying degree, and sometimes the dog may not be affected at all. Whether the dog will get clinical symptoms or not is primarily depending on the grade of dysplasia, but also on the entire construction and function of the dog. There is no doubt

that the right kind of exercise is important. A dog with a mild form of HD will usually not show clinical signs, and will be able to live a normal life. If the dog has a medium degree of dysplasia there is a greater risk of developing symptoms. The time at which these symptoms first start to occur varies greatly. Some dogs with a medium degree can start to show signs of decreased range of motion around age 4-5 without any signs that the condition is painful for the dog. Other individuals can show symptoms earlier and some may not be affected at all. Excessive exercise, such as long walks in deep snow and allowing the dog to pull in the leash for a long period, is not recommended. On the other hand, one has to be aware that dogs with a medium degree of dysplasia may have obvious clinical symptoms and pain related to the defect.

For dogs with a strong degree of HD, the risk for developing problems with their hip joints is greater. For some dogs this defect is clearly disabling, and euthanasia may be the best option in some cases. One should always be aware that these dogs may also function normally and live a long and healthy life without signs of pain. Thus it is important not to treat the dog only based on the radiological signs.

A dog with hip dysplasia of varying degrees needs the correct kind of exercise. It is important that muscles are built and that joints, ligaments and tendons are not stressed. The amount of ***exercise*** should gradually increase from the puppy stage till they are adults, and walking on asphalt and in deep snow is not recommended. Neither is walking in stairs below the age of 3 months. Another important factor is the ***nutrition*** and body condition, and dogs that are of high body condition score have an increased load on the skeleton.

Regarding the prevention of hip dysplasia, ***breeding to reduce the prevalence*** of categorically scored hip dysplasia based on radiological imaging ***has had limited success***. The phenotypic expression of HD is affected by ***non-genetic factors***, implying that the phenotype of HD is not a particularly accurate indicator for the genotype. Hip dysplasia remains a significant problem, despite the work done to decrease the occurrence of the disease. This is partly due to its ***complexity*** as a ***polygenic disorder influenced by environmental conditions***. Canine genes associated with etiological aspects of hip dysplasia have been ***identified***, and several researchers have identified quantitative trait loci (***QLTs***) for different phenotypes on several chromosomes.

As a consequence of limited success of breeding programs using selection based on phenotypic records, researchers have found that selection based on best linear unbiased prediction (BLUP) gives a substantially faster genetic improvement. The use of BLUP causes an increased in the rate of inbreeding, but by using a ***combination of BLUP and OCS (optimum contribution selection) an overall genetic improvement will be achieved***.

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