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CURRENT GENOMICS (GENETIC MARKERS) OF CANINE HIP DYSPLASIA

A REVIEW OF LITERATURE

By

Tal Kornblut

SUPERVISORS:

Professor László Zöldág

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1. Introduction

1.1. Overview of Canine Hip Dysplasia

Canine Hip Dysplasia (CHD) is one of the most common hereditary orthopedic conditions affecting dogs worldwide. This complex disorder primarily affects large and giant dog breeds (German shepherd, golden retriever, etc.). Although it is not common, CHD can occur in small breed dogs as well. CHD is characterized by an abnormal development of the coxofemoral joint (hip joint), in young patients, subluxation or complete luxation (separation of the head of the femur from the acetabulum), and in old patients, degenerative joint disease (DJD) will be seen [1].

CHD can lead to chronic pain, reducing life quality and in severe cases the only solution may be euthanasia due to the pain and inability of the dog to use the hindlimbs. The importance of CHD is not only due to animal welfare but also can be a problem for breeders, veterinarians and dog owners.

Canine hip dysplasia is a complex condition that relates to genetic predisposition and environmental factors. CHD is polygenic inheritance which external factors can trigger its progress (e.g., nutrition, exercise, weight, growth rate). All of those factors can cause CHD to be more challenging to manage and prevent. As CHD is polygenic condition it is harder to eradicate from breeding. Despite many years of research and breeding programs aiming to reduce its incidence, CHD still is common.

1.2. Importance of genomics of CHD

Researching and understanding the genomics of CHD can be the most important way to reach an effective prevention and help with early diagnosis and therefore better management strategies. As research in canine genetics advances, there is growing hope that improved molecular tools will enhance our ability to identify at-risk animals earlier and make more informed breeding decisions. This thesis aims to explore the current state of knowledge regarding the genomics of CHD, with a particular focus on genetic markers and their potential applications in combating this pervasive condition.

2. Canine Hip Dysplasia: An Overview

2.1. Anatomy of CHD

The anatomy of the hip joint has a significant role when discussing CHD. Knowing which structures are visible and which are palpable on the dog and using this knowledge for physical examination. Interpreting radiological images requires a deep understanding of the physiological anatomy. Having a deep knowledge of hip joint anatomy is key for surgical understanding.

The hip joint (articulatio coxae or coxofemoral joint) is a ball and socket joint which is composed of the articulation of the femoral head with the acetabulum. As a ball and socket joint there is a wide range of motion, but the hip muscles restrict the range of motion. The hip joint plays a crucial role in weight-bearing and locomotion in dogs [2].

Acetabulum:

The acetabulum is composed of the three pelvic bones (ilium, ischium, pubis) and a fourth small bone, the acetabular bone. These four bones form the cotyloid cavity, commonly referred as the acetabulum [2], [3].

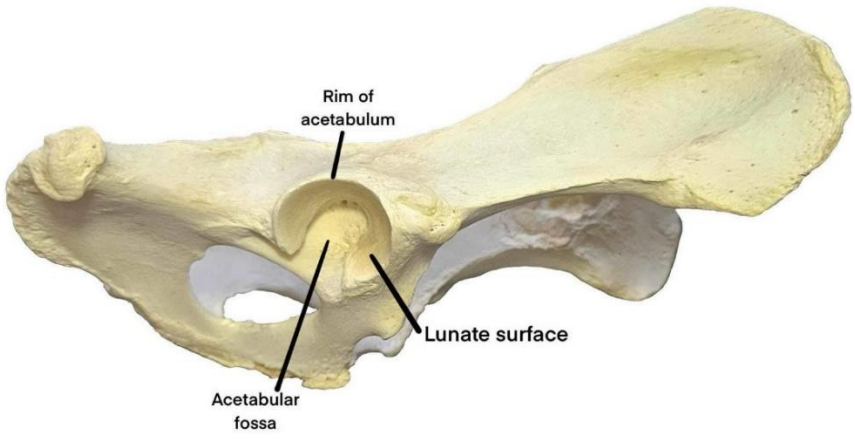

Figure 1: The acetabulum: showing the rim of the acetabulum, lunate surface and acetabular fossa.

At the rim of the acetabulum (Figure 1), there is the acetabular lip (labrum acetabulare), made of fibrocartilage, this structure enhances the depth of the acetabulum. The acetabular lip extends over the acetabular fossa and forms the transverse acetabular ligament (ligamentum transversum acetabuli). The joint capsule is attached to the acetabular lip, and the acetabular lip not only deepens the socket but also increases the contact area with the femoral head, providing additional stability to the joint. The articulating surface of the acetabulum is the lunate surface (facies lunata), which is covered with hyaline cartilage, while the non-articulating surface is the acetabular fossa (Figure 1), [2], [3].

Femur:

The femur is a long bone that has a main function in posture and locomotion. The femur can be divided into three sections:

1. Proximal extremity (caput ossis femoris), bearing the head of the femur.
2. Shaft of femur (corpus ossis femoris).
3. The distal extremity.

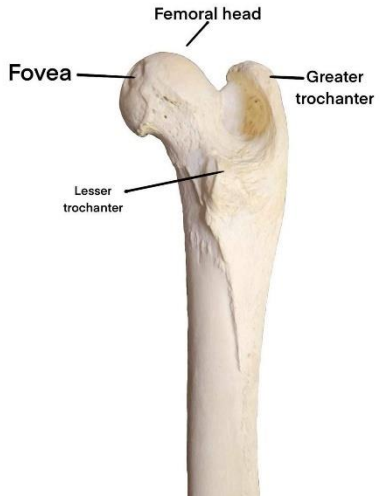

Figure 2: proximal extremity of the femur. On the medial side the fovea on the femoral head is labeled.

On the proximal extremity of the femur, the femoral head is positioned medially with the fovea for the ligament attachment and laterally, the greater trochanter is found (Figure 2). The greater trochanter can be palpated on the dog's hip and used to perform palpation tests for joint laxity [3], [1], [2].

The acetabulum and the femur are attached by the intracapsular ligament of the femoral head (ligamentum capitis ossis femoris). This ligament extends from the fovea of the femur head (Figure 2), goes through the acetabular notch, to the acetabular fossa [2], [3]. The ligament of the head of the femur is called in some literature the round ligament or teres ligament.

The femur head is rounded and fits the acetabulum closely, while allowing a wide range of motion. In hip dysplasia the normal development is disrupted leading to abnormalities of the joint and results in degenerative joint disease [1].

2.2. Pathogenesis and pathophysiology of CHD

The pathogenesis of CHD starts with a genetic predisposition, seen especially in large breed dogs but can affect all dog breeds. This genetic predisposition, together with environmental factors such as increased growth of puppies can cause developmental abnormalities in the hip joint.

Dogs with a genetic predisposition to CHD are born with apparently normal hips, abnormalities of the hip joint will start to develop within the first three weeks of life. Currently, the two main proposed etiologies for CHD are hip laxity (excessive movement in the hip joint) and abnormal progression of endochondral ossification (abnormal development of the acetabulum and femoral head). These abnormalities will be seen starting at about 1-2 months old puppies [4], [1], [5].

Environmental factors such as nutrition, increased body weight, and exercise can contribute to the deterioration of the hip joint [1].

The ligament of the femoral head is the main supporting structure of the hip joint in puppies until 1 month of age. After the first month of life, the joint capsule will be the main supporting structure in healthy dogs. In a healthy joint capsule, after bearing pressure it will go back to its original shape compared to lax capsule where the pressure will cause further deformation [5], [4], [6].

Due to the development of subluxation, where the hip joint is loose, the femoral head partially slips upward, stretching the joint capsule. This causes pain and limping. The acetabulum is made of soft, spongy bone (cancellous bone) which changes shape over time due to the continuous up-and-down pressure from the femoral head. This piston-like action tilts the acetabular surface from flat to more upright. As a result, the dog's weight presses on a smaller part of the joint, causing more damage [1].

Over time, the instability of the hip joint will develop and as a result degenerative changes will occur to the hip joint; synovitis (synovial inflammation). Due to the instability of the joint,

osteophytes will appear and due to the increased stress of the bone, subchondral sclerosis can also be apparent [4], [6], [7].

Shallow acetabulum, deformed femur head are common changes seen in dogs with hip dysplasia. With those changes the femur and the acetabulum no longer fit correctly. This results in subluxation and luxation of the joint.

While there is no exact timeline for the progression of CHD there is an approximation of the progression with juvenile patients. It should be noted that there are many intrinsic and extrinsic factors that can influence the progression of CHD and therefore clinical signs, and clinical findings will vary [7].

At the early age of 1 week old puppies with CHD that shows hip laxity, a larger acetabulum rim may be already present. This indicates less coverage of the femoral head in the joint, the femoral head no longer fits the acetabulum closely. At about 8 weeks old, subluxation (partial dislocation) of the hip joint may be apparent as well as delay in the ossification of the craniodorsal acetabular rim. By the age of approximately 2 months old the femoral head subluxation will increase, and the joint abnormalities will continue to increase as the puppy grows. At 5 months old more abnormalities will appear, such as microfractures and degeneration of the articular cartilage, thickening and inflammation of the joint capsule as well as changes to the tendinous insertions (contributing to the joint instability) of the joint [7].

Collagen ratio differences have been seen in dogs with CHD compared to healthy dogs. Dogs with CHD have a higher ratio of collagen type III to type I, indicating a weak joint capsule. The reason for this increase in ratio still remains unknown but it is theorized that a response to capsular injury [5]. The collagen type I is needed for the strength of the joint capsule. The mean ratio is higher in dogs with high prevalence for CHD compared to dogs with low prevalence; However, when comparing the dogs in the high prevalence group there was no significant difference between dogs with dysplastic hips to those with normal hips. Therefore, it is safe to assume that the increase in ratio can have a part in the pathological changes of

CHD, but it still remains unknown whether this is a primary alteration or a secondary process due to fibrosis of the joint in dysplastic hips [8], [9].

Development of OA (osteoarthritis) is a secondary process in dysplastic hips and is an irreversible outcome of CHD. Degenerative changes of the joint will occur as a result of the laxity and subluxation. Due to an increase of force over a smaller area will cause wear and tear of the joint, this will trigger a release of inflammatory mediators and destructive enzymes. Water will accumulate in the joint, and damage to collagen structure, as a result there will be fibrillation and decrease to the joint stiffness and therefore the joint will be more exposed to injury. The continuous inflammatory process and the mechanical stress on the joint capsule and the bones will cause remodeling . The femur head and the dorsal acetabular rim will become denser, and the cartilage will thicken as an attempt at compensation. Eventually the cartilage won't be able to keep up with the healing demand and the subchondral bone will be exposed [8].

2.3. Clinical signs

Canine Hip Dysplasia will more commonly be bilateral but can also present as unilateral and is presented equally in both male and female patients [10]. Clinical signs vary depending on the patient's age. Two different types of patients are affected by canine hip dysplasia: juvenile with hip laxity and adult dogs with osteoarthritis [1], [11]. The clinical signs won't always correlate with the radiographic findings, in some cases clinical signs won't be noticeable but the joint abnormalities will be apparent in radiographic images [6].

Clinical signs depend on the extent of joint laxity and the degeneration of the hip joint. In the early stages of CHD, the clinical signs will be mostly related to the hip laxity, while in later stages the clinical signs will be mainly due to the degeneration of the joint. Early clinical signs might start at about 5 months old puppies, where they may experience pain and discomfort during or post exercise. As those puppies will grow and develop, the clinical signs will increase due to the progression of the deterioration of the hip joint [10].

Clinical signs [12]:

- Difficulty rising after rest (seen in both juvenile and adult patients).
- Exercise intolerance (seen in both juvenile and adult patients).
- Lameness of hindlimbs: in juvenile patients can be intermittent or continual. In adult patients with degenerative joint disease, lameness will be mainly post-exercise.
- "Bunny hopping" gait (the dog lifts both hindlimbs together mainly when trying to run).
- "Boxy hips" – due to the luxation of the femoral head, the hips will appear a more square-like shape.
- Avoiding complete extension and flexion of the hip joint, reluctant to jump, climb stairs.
- Atrophy of pelvic musculature (seen in adult patients with degenerative joint disease). Usually due to this atrophy in the hindlimbs, the increased load on the forelimbs will cause an increase in the shoulder's musculature.

Over time, as the joints deteriorate, a general worsening might take place and even get to a stage where the dog will need assistance to get up and won't be able to stand and walk without assistance.

The veterinarian will perform a lameness evaluation in order to see the type of lameness and to evaluate the gait. During this evaluation, the lameness will worsen during or after an increased activity [11], [10].

2.4. Diagnosis

The clinical signs of CHD are non-specific and therefore insufficient for a definitive diagnosis. Taking history of the clinical signs while considering age and breed, then performing physical examination and diagnostic imaging are necessary to reach a conclusive diagnosis [10].

History and clinical signs:

Clinical signs may appear in puppies under one year old, and in other cases clinical signs may appear in adult dogs, depending on the progress of the deterioration of the hip joint. When a patient arrives with clinical signs matching CHD (mentioned previously), the veterinarian should perform a thorough physical examination [10].

Physical examination:

The physical examination includes: visual assessment, lameness and posture evaluation, palpation tests and evaluating the movement of the joint (laxity/rigidity and pain).

Visual examination – the veterinarian will assess the musculature of both the hindlimbs and forelimbs. The findings will differ between juvenile and adult patients: In juvenile patients the hind limbs musculature will be poorly developed while in adult CHD there will be atrophy of the hindlimb musculature, indicating the decrease in muscle mass and weakening of the hindlimbs. As a result of the deterioration and pain of the hip joint, the dog will rely more on the forelimbs, causing a more developed forelimb musculature [10].

Lameness and posture evaluation will include [10], [12]:

- Hindlimbs posture while standing – may have the hindlimbs in a narrow stance.
- Standing after rest – may show difficulty standing after laying.
- Walking, trotting, ascending stairs – CHD patients may show an increase in lameness after exercise, reluctance to walk up the stairs or reluctance to walk/trot all together.

Palpation techniques – for the assessment of juvenile CHD, the Barden and Ortolani tests are used, these tests provide a subjective assessment of joint subluxation. These palpation techniques are done under general anesthesia. For a more objective evaluation, radiological imaging is performed to quantify the degree of subluxation. These tests are most appropriate for juvenile patients up to approximately 2 years of age, before the onset of fibrosis in the joint. In adult CHD patients there will be a decrease in joint laxity [12].

Barden test, used to test for joint laxity in a lateral direction. The Barden test is performed while the dog is in lateral recumbency, moving the joint upwards (lateral direction of the joint). One hand of the veterinarian will be on the hip joint, to feel the subluxation, and the other hand will be on the medial side of the leg while holding the stifle with the thumb, lifting the hip joint and pressing the greater trochanter. A displacement of the femur head that is over 2 millimeters is considered as a positive result of the test.
Ortolani test: starting with Barden test to subluxate the hip joint, then abducting the leg to feel and see when the femur head will return to the acetabulum [1], [10], [7], [12].

Testing the joint movement – the veterinarian will test the movement of the joint by extension, flexion, abduction and adduction. Both adult and juvenile CHD patients will experience pain and discomfort due to the joint deterioration. However, adult CHD patients will also present a reduced range of motion in the affected hip joint [10], [11], [1].

Radiographic diagnosis

Radiography remains the gold standard for diagnosing CHD. Radiographical imaging provides precise information about the state and progression of the primary joint laxity and the secondary joint degeneration, allowing veterinarians to assess the joint condition [7], [10].

Radiographical screening is also used to gather phenotypical data for selective breeding programs. This is done in order to reduce the incidence of CHD in future generations by identifying dogs with healthy hip conformation for breeding.

The most common radiographic view used in CHD diagnosis is the ventrodorsal projection with extended hip joints (as seen in Figure 3). In this technique the dog is positioned on its back with the hindlimbs extended while rotating the hindlimbs medially to center the patella over the trochanter grooves (making sure both hindlimbs are in the same position). The aim of this position is to have symmetrical pelvis, parallel femurs and the patellae positioned centrally. This view gives a good visualization of the relationship between the femoral head and the acetabulum, as well as the conformation of each structure [10], [12].

Stress radiography can be combined with standard projections to provide additional diagnostic information. In stress radiography the hip joint is displaced, there for helping the assessment of hip laxity. It is important to note that stress radiography is done under general anesthesia as it is a painful technique.

Obtaining a high-quality radiographic image depends on several measures that should be taken.

- General anesthesia can help acquiring higher quality image be eliminating blurriness due to movement. General anesthesia will also help for relaxation of the muscles and by that easier positioning.
- Proper positioning of the dog, usually by manual restraint. If available, it is recommended to use mechanical immobilization devices to reduce radiation exposure to staff.
- Proper equipment

Acquiring a good quality radiographic image is important in order to aid the accurate diagnosis and assessment of CHD [13], [11], [10].

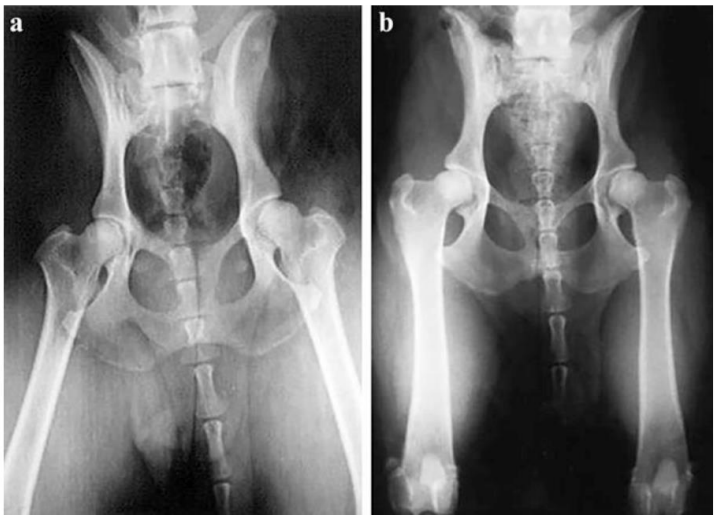

Figure 3 ventrodorsal view of a dog positioned at a dorsal recumbency [10] a) incorrect positioning, b) correct positioning.

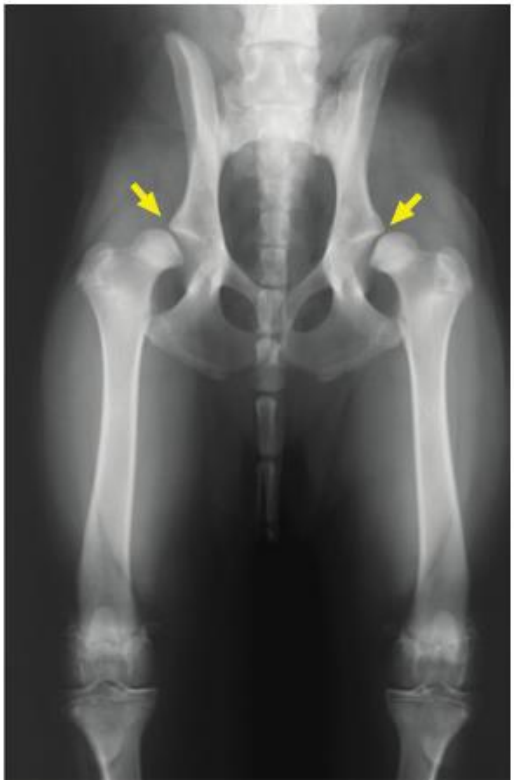

Figure 4 radiographic imaging showing subluxation of the femoral head (arrows) – indications of hip dysplasia [11].

The FCI (Federation cynologique internationale) has an official classification in order to grade canine hip dysplasia in a universal way, using radiographical imaging [14].

Norberg angle (NA): on a ventrodorsal x-ray of the hip, a line is drawn between the center of the two femoral heads, a second line is drawn from the center of the femoral head to the cranial rim of the acetabulum, and the angle formed between these lines is the NA [10].

The grading of the FCI is indicated from grade A (normal hips) to grade E (severe dysplastic hips (Table 1 grading of hip dysplasia by the FCI system).

A study by Merca et al. (2020) found that there are differences in hip measurements in puppies that later in life developed hips with grading A compared to grading B, meaning that veterinarians can predict development of future hip conformation in puppies [15].

From this study it is safe to assume the success of using the FCI grading for accurate diagnosis and predicting CHD from puppies.

A study of 2,885 dogs found that the diagnosis of CHD based on radiographic screening become more accurate with older dogs. The found a difference in the prevalence of CHD between dogs that were 36 months old or younger compared to dogs over than 36 months old, the older dogs had more incidences of CHD. This indicates that some cases may be missed in younger dogs when using radiographic techniques [16].

Arthroscopy – surgical procedure used to diagnose joints. Inserting the arthroscope to the joint give the possibility of good visualization of the joint structures and any pathological changes. Unlike radiographic imaging, arthroscopy does not have specific criteria for diagnosis [1].

FCI classification of CHD	
Grade A **No sign of hip dysplasia.**	NA is 105°. The femoral head is well centered in the acetabulum. Joint space is narrow and even. The craniolateral rim – well defined and rounded. No signs of OA.
Grade B **Near normal hip joints.**	NA is between 100-105°. Femoral head is centered in the acetabulum. The center of the femoral head is medial to the dorsal rim of the acetabulum. No signs of OA.
Grage C **Mild hip dysplasia.**	NA is about 100°. The femoral head is not centered well in the acetabulum. The craniolateral rim is slightly flattened. Subluxation of the femoral head can be present. OA changes might be present.
Grade D **Moderate hip dysplasia.**	NA is more than 90°. The femoral head is not centered well in the acetabulum. Obvious diverging of the femoral head from acetabulum, subluxation Flattened craniolateral rim. OA changes may be present.
Grade E **Severe hip dysplasia.**	NA is less than 90°. Marked dysplastic changes of the hip joint. Remodeling and deforming of acetabulum and/or of the femoral head. Luxation or distinct subluxation. Signs of OA may be present.

Table 1 grading of hip dysplasia by the FCI system [14].

2.5. Treatment and management

Canine Hip Dysplasia can cause severe pain and discomfort in patients and subsequently cause lameness and even reluctance to walk and stand. Therefore, it is important to understand the treatment options and by that decide the best option for each patient. The progression of CHD is unpredictable and so it can be challenging choosing the most beneficial treatment for a patient. There is no gold standard for CHD treatment and each case should be considered individually [17].

Early intervention by early diagnosis is of high importance. With early intervention it is possible to prevent the future complications of CHD and by that increase the life quality and even life expectancy of the patient. As mentioned previously, the clinical signs in the later stages of the progression of CHD, joint pain can cause reluctance to walk and even stand, therefore preventing those consequences improves the life quality.

There are two main types of treatment, surgical and conservative, the veterinarian should suggest a treatment plan after considering the factors influencing the treatment. These factors include: age of the patient, pain level, findings of the physical examination and radiographic findings (signs of OA and to what level), and the financial ability of the owner as some treatments can be expensive [1], [17].

Conservative treatment:

The conservative treatment of CHD is mostly a palliative treatment, relieving pain and reducing the influencing factors and thereby slowing the progression of the condition. This type of treatment requires several approaches, nutritional changes, physical therapy, and drug administration.

Administering the anti-inflammatory and analgesic drugs, combined with supplements, appropriate diet and physical therapy while it can slow the progression of CHD it does not reverse the pathological changes the joint already has [10], [18].

It is important to note that due to the unpredictable progression of CHD, it is difficult to have a definite estimation whether a conservative treatment is working or not, especially in patients with minimal clinical signs and diagnostic findings [17].

The use of non-steroidal anti-inflammatory drugs (NSAIDs) can alleviate the pain associated with arthritic joints as a result of CHD progression [10], [7]. Some NSAIDs can cause suppression of joint regeneration and so it is important to administer the appropriate NSAIDs. Some of the NSAIDs appropriate for joints are piroxicam, meloxicam, carprofen, but side effects should still be considered, performing check-ups for nephrotoxicity, platelet aggregation, gastric ulcers and so on [17], [19]. It is important to remember that due to the fact that NSAIDs reduce pain, the patient might try to move and exercise more and by that cause more damage to the joint. Therefore, veterinarians should advise the owner of the patient to make sure the patient rests enough and to restrict exercise [1].

Corticosteroids can be beneficial for cases where OA already developed, to reduce inflammation in the joints and suppress the immune system [10].

Pharmaceutical treatment is mainly short-term, relieving the pain, reducing inflammation, with this treatment it is also recommended to restrict exercise. Later specific exercise such as swimming is advised, helping for muscle building, improving range of movement of the joint; Therefore, strengthening the joint and slowing the degeneration of the joint [1], [4].

Maintenance of healthy body weight is considered one of the most important and useful conservative methods to reduce clinical signs associated with CHD (and joint pain in general). This is due to the fact that in overweight and obese dogs there is higher pressure on the joints, contributing to the inflammation and degeneration of the joints [7].

Nutrition and supplements: a special diet to reduce weight for obese and overweight patients should be planned by the veterinarian in order to make sure that all nutrients are still provided. Supplements such as essential fatty acids (omega 3) to reduce inflammation, glycosaminoglycans for cartilage regeneration and antioxidants are recommended for arthritic patients. Glucosamine and chondroitin can reduce inflammation, promote the healing process of the joint, help with water retention in the cartilage and therefore slow the progression of

joint damage, these supplements are used for both animals and humans with joint degeneration [10].

Physical rehabilitation post-surgery or together with conservative treatment can help decrease the pain, increase strength and improve the range of motion of the joint [20].

Surgical treatment:

Besides conservative treatment, there is the possibility of surgical treatment. While surgical treatment potentially can repair the joints and be a particularly good option with a good prognosis, it can be very expensive in case the owner does not have an insurance that will cover the costs [1], [7].

Early surgical treatment can have a good long-term prognosis, but some owners may prefer to start with the conservative treatment and only consider surgery if the condition worsens and the conservative is not working. Conservative treatment can be successful, while not fixing the joints – as in surgery, it can help patients live comfortably. Surgery is not only indicated for patients whom conservative treatment did not work, but it can also be an option for juvenile patients that are intended for physical work, as well as for patients that their owners wish to have a higher chance of good mobility of the joint long-term [1], [7].

There are numerous surgical procedures for CHD; the decision on the type of surgery depends on numerous factors, age, state of the joints, general health of the patient. Some surgeries aim to prevent OA while other procedures are aimed at fixing the joints [7].

While in young patients the clinical findings are due to the subluxation or complete luxation of the hip joint, in adult patients the clinical findings are consequences of fibrosis of the hip joint due to OA. Treatments for advanced and chronic progression of CHD, whether conservative or surgical, tend to be more expensive and are less effective. Early surgical treatment are aimed for the prevention of OA and therefore early diagnosis and treatment is more advised. Although early surgical procedures have better results long term, it is important to mention that these procedures still have their risks and a long recovery [20], [10].

Surgical procedures [1], [10], [12]:

1. Juvenile pubic symphysiodesis.
   This procedure can prevent future complications of CHD, directed for puppies under 20 weeks of age with hip laxity, before the development of arthritic changes. Electrosurgically heating the pubic symphysis causes premature closure of pubic symphysis, preventing further growth of this area. The rest of the pelvis continue to grow normally, and subsequently the acetabulum will rotate ventrolateraliy, increasing the coverage of the femoral head – improving the articulation of the hip joint. This procedure prevent further complications of CHD.
2. Double and triple pelvic osteotomy – increasing the coverage of the femoral head
   This procedure is prophylactic as well and used in puppies younger than 10 months old with severe joint laxity. This is an invasive surgical procedure with a long recovery time. Cutting through the pelvic bones in order to the orientation of the acetabulum and as a consequence improving stability of the joint, reducing pain and preventing osteoarthritic changes.
3. Total hip replacement – a salvage procedure, where the whole hip joint is removed and replaced. This procedure is indicated when the coxofemoral joint is too damaged and cannot be repaired. 3 implants are used to replace the joint, an acetabular cup (implanted on the pelvis), femoral stem with neck (implanted in the femur), and a femoral head (placed on the femoral head). This procedure can be cementless, for medium and large breeds, or cemented for small breeds.
4. Femoral head ostectomy – is a salvage procedure as well. This procedure is indicated when conservative treatment was unsuccessful and/or for smaller breed dogs with severe pain and no other surgeries are available for the patient. In this procedure the head of the femur (and neck in some cases), is surgically resected. While alleviating pain, the patient will have a restricted range of motion in the joint and a decrease in joint stability. This is a last resort, when total hip replacement is not possible.

2.6. Prevalence in different dog breeds

While CHD can occur in all dog breeds, some breeds have higher prevalence of CHD. [10]

The prevalence of CHD in dogs overall is unknown, and in specific breeds the reported prevalence has a wide range. This may be due to the fact that there is no obligation to report CHD to any official office [8].

While CHD can affect all dog breeds (with a higher prevalence in large breeds), studies have shown that there is a variation of the manifestation and progression of CHD between breeds. For instance, Merca et al. (2020) found a difference in puppies' hip measurements between Labrador Retrievers and Golden Retrievers. This finding suggests that breed-specific patterns in hip development exist and therefore it is important to know the breed characteristics when diagnosing CHD [15].

While CHD is considered mainly a large breed genetic disease, the OFA statistics show that the top 3 dog breeds that were found with dysplastic hips are: Olde English Bulldog with 73% (216 with dysplastic hips out of 295 dogs evaluated), Pug was ranked second with 72% (889 with dysplastic hips out of 1232), and third is the Bulldog breed with 71% (1073 with dysplastic hips out of 1521 evaluated). German Shepherds ranked 46th with 21% of cases with dysplastic hips, but 143,158 dogs were evaluated, and 29,326 dogs were diagnosed with dysplastic hips. Golden Retrievers are ranked 51st with 19%, evaluating 185,053 dogs out of which 35,962 were diagnosed with dysplastic hips [21].

It is important to look not only at the percentage of diagnosed patients but also at the number of dogs evaluated. Because German Shepherds and Golden Retrievers are known to be more prone to CHD, they are evaluated more often and from a younger age, while breeds that are not known to have CHD will be evaluated only in cases of clinical signs (lameness, reluctance to stand and other clinical signs).

A study by Rettenmaier et al. (2002) at a veterinary teaching hospital searched for the prevalence of CHD of dogs with no or minimal radiographic screening of both pure-bred dogs and mixed breeds. Radiographic screening for a 5-year period and 2885 dogs were examined. They found that the general prevalence of CHD in general dog population was 19.3%.

interestingly, they did not find a significant difference between the pure-bred (19.7%) and the mixed breed dogs (17.7%), this finding breaks the common belief that mixed breed dogs are less prone to CHD. Also, no significant difference was found between female and male populations [16].

The finding of the similar prevalence between mixed and pure-bred dogs is significant, as breeding programs for the decrease of incidence of CHD are only applied to pure-bred. A prevention strategy should be studied for mixed breeds as well.

A study in France by Baldinger et al. (2020) examined the prevalence of CHD in 10 dog breeds over a 20-year period. A significant variation was found when comparing the breeds in the study, with prevalence ranging from 5% in Siberian Huskies to as high as 51.9% in Cane Corsos. During the 20-year period they found a decrease in the prevalence of 6 breeds out of the 10 studied, out of which 4 breeds showed a significant decrease. One breed (Siberian Husky) showed an increase of prevalence [22].

In order to determine an accurate prevalence more evaluation should be made with randomized groups at the same ages, and with genetic testing.

3. Genomics of Canine Hip Dysplasia

3.1. Genetic basis of CHD

Canine Hip Dysplasia is a polygenic disorder (multiple genes are responsible for it), this is one of the reasons that cause breeding out CHD to be so difficult. The heritability of CHD varies between different dog breeds. While genetics play a significant role in developing CHD, environmental factors (external influence) also contribute to the expression of CHD. The polygenic inheritance of CHD implies the effect of multiple genes, each contributing a small effect to the overall phenotype, and many alleles scattered throughout the genome are involved in the development of CHD. For this reason, simple genetic tests based on a single marker are unlikely to be effective in predicting and preventing CHD [8].

A study by Edwards et al. (2018) combined data on CHD on Labrador Retriever populations from UK and US in order to try to enhance the genomic prediction accuracy. They used the GBLUP (genomic best linear unbiased prediction) to analyze the data. The study's results were surprising, when the data from the two countries was combined there was no significant increase in the prediction accuracy, compared to single-country data. The genetic relationship between Labrador Retriever population in UK and to the population in US was low, which explains the lack of benefit when combining the data. This finding highlights the genetic complexity of CHD across different populations and suggests the need for population structure in genomic studies. This suggests the need for data of closely related populations in order to diagnose CHD based on genetic testing [23].

A recent validation study by Mikkola et al. (2021) examined 46 genetic markers that were previously reported to be associated with CHD on 1570 dogs from 10 different breeds. They categorized the dogs into cases based on FCI scoring system. The study validated successfully 21 different loci on 14 chromosomes, where 20 loci have breed-specific associations, and one locus was identified as across breed analysis. This finding confirms the complex genetic nature of CHD and highlight the that both breed-specific and shared genetic factors are contributing to this condition [24].

3.2. Candidate genes and genetic markers associated with CHD.

A study by Fels and Distl (2014) on 843 German Shepherd dogs, five single nucleotide polymorphisms (SNPs) on four chromosomes were investigated for association with CHD, chromosomes 19, 24, 26 (one SNP on each) and on chromosome 34 (2 SNPs). The study found a significant linkage between CHD and the SNPs on chromosomes 24, 26, 34, one on each (see Table 2). Those three SNPs are located within or close to genes involved in joint network, regulation of bone formation, osteoclast activity, chondrocytes proliferation and differentiation. The study also found higher numbers of dogs affected by CHD when they had more than 1 of those SNPs. The researchers also found a joint network between the three candidate genes, involved in bone formation. This study can give a more accurate genetic screening and therefore help selective breeding programs in order to reduce the incidence of CHD [25].

Breed	*Chromosome*	*SNP*	*Gene near the SNP*
German Shepherd	24	BICF2S2367279	SRC
	26	BICF2P281364	KSR2
	34	BICF2P1086886	TRIO

Table 2: Summery of the three SNPs on chromosomes found to have linkage to CHD, and nearby candidate genes [25]

A study by Bartolomé et al. (2015) on 755 Labrador Retrievers researched SNPs associated with CHD. The researchers combined a genome-wide association study (GWAS), analyzing over 170,000 SNPs, and also chose over 700 SNPs on candidate genes and quantitative trait loci (QTL) for CHD. The candidate genes selected are related to molecular processes of CHD and/or OA such as cartilage degradation, bone remodeling, genes associated with cartilage and bone diseases in humans and so on. They developed a genetic predictive model for CHD that included 7 SNPs that showed good accuracy. The SNPs in this predictive model were found near genes involved processes related to CHD development (see Table 3). For example, one of the SNPs were located in a gene involved in chondroitin sulfate biosynthesis (chondroitin

sulfate is an important component of cartilage, providing elasticity). Other SNPs were located near genes related to bone metabolism, extracellular matrix metabolism and muscle mass determination. These findings suggest the involvement of these genes in the pathogenesis of CHD [26].

Breed	*Chromosome*	*SNP*	*Gene(s) near SNP*	*Gene functions related to CHD*
Labrador retriever	4	BICF2P772455	CHST3	Plays a role in chondroitin biosynthesis, important for cartilage function.
	3	BICF2G630339806	CHSY1 ADAMTS17	CHSY1 – also plays an important role in chondroitin biosynthesis ADAMTS17 – associated to osteoporosis and OA in humans.
	18	BICF2S230609	FGF4	Extracellular matrix metabolism Studies in mice suggest relation in embryonic distal limb morphogenesis.
	20	BICF2G630227898	RAB7A	Related to bone-resorbing osteoclasts.
	10	BICF2S2452559	PKCE	Involved in bone remodeling.
	7	BICF2G630558239	SMYD3	Potentially involved in skeletal muscle atrophy of the hind limb.
	12	BICF2P548082	No candidate gene found	

Table 3: Summery of the three SNPs on chromosomes found to have linkage to CHD, and nearby candidate gene with their functions related to CHD [26].

A more recent study from 2021 managed to validate 21 genetic markers with association to CHD. This validation study provided significant insights into candidate genes and genetic markers associated with CHD. The study found an enrichment of candidate genes involved in neddylation pathway in the validated loci. Neddylation takes part in many cellular functions and was linked to inflammatory arthritis. This finding of the potential involvement of neddylation in CHD opens more possibilities for research on the process of CHD and the researches recommend that this should be explored more [24].

Breed	*Chromosome*	*SNP*	*Gene near the SNP*	*Gene function*
Across-breed, Bernese Mountain dog	14	ss7212922135	CTTNBP2	Found to be associated with juvenile idiopathic arthritis and idiopathic osteonecrosis of the femoral head.
			WNT2	Development and progression of OA.
German Shepherds	1	ss7212922118 ss7212922120	NOX3	May be part of the initiation of articular cartilage degradation.
Across-breed, German shepherd	26	ss7212922151	KSR2	Associated with obesity in humans and mice.
			NOS1	Abnormal skeletal muscles.
German Shepherd	33	ss7212922122	ABI3BP	Joint hypermobility in humans.
Across-breed	37	ss7212922139	NRP2	involved in vascular endothelial growth factor.

Table 4: highlighted SNPs on chromosomes found to have linkage to CHD, and nearby candidate gene with their functions related to CHD [24].

3.3. Molecular Diagnosis and Screening

Using radiographic screening with FCI or OFA scores can produce false negative results, and as a consequence use dogs who had false negative result for breeding. These dogs with false negative results are therefore allowed for breeding and consequently pass down genes that can promote CHD [4]. Using molecular diagnosis for CHD can be more accurate and help to decrease the prevalence of CHD faster and in a more efficient way.

A study by Rettenmaier et al. (2002) reported a higher number of cases in dogs over 36 months old compared to younger dogs; radiographic screening was used for the CHD diagnosis. This finding shows that radiographic screening might not be the best option for CHD diagnosis in younger dogs. While radiographic screening is the gold standard for CHD diagnosis nowadays, the advancements in molecular biology and genetics have opened good possibilities as diagnostic and prevention tools. By using molecular diagnosis, there can be a possibility for an earlier diagnosis of CHD and therefor to be able to treat, manage and prevent in a more successful way [16].

Genomic statistics methods

A recent study by Jiang et al. (2021) tested two genetic prediction models for CHD and rupture of cranial cruciate ligament, as both are complex inherited orthopedic traits. This study aimed to find the more accurate model in order to improve breeding section programs in the future. They used the GBLUP and BayesC models. GBLUP assumes all genetic markers can have some effect on the trait and uses genetic matrix to make predictions. BayesC, on the other hand, try to identify the most important markers of the trait and uses it for its predictions. They found that using GBLUP and BayesC, had no significant differences when predicting CHD. The researchers suggests the need for larger datasets within breeds and across breeds in order to achieve higher accuracy [27].

More studies are examining specific genes that may take a part of this polygenic trait and by successfully identifying these genes it can be possible to use molecular diagnosis in order to breed out CHD and to decrease the progression by early management.

Challenges in genetic testing:

While genetic testing appears like a promising method for an accurate early diagnosis of CHD, recent research from 2020 highlights the significant challenges in developing reliable genetic tests. Dysgen test is a genetic test for CHD, based on seven SNPs, for Labrador Retrievers that was developed using Spanish Labrador Retrievers. The study by Bruun et al. (2020) evaluated the effectiveness of the Dysgen test in a population of Danish Labrador retrievers. Dysgen test, when applied to 39 Danish labrador retrievers with known radiographic hip scores, showed no significant correlation with the dogs' actual hip status. This finding may be due to genetic differences between populations, Danish compared to Spanish and breed line differences. The researchers conclude that so far genetic testing cannot stand alone and should be confirmed by radiographic evaluation. They also point out the need to validate SNPs data in relevant populations before using them for breeding programs [28]. A study by Edwards et al. (2018) also suggests the possibility of a population specific genetic background (Labrador Retrievers from UK and US) [23].

4. Prevention Strategies for Canine Hip Dysplasia

4.1. Breeding programs and selection criteria

It is well established that CHD is a polygenic condition therefore, using breeding programs in order to reduce its incidence can be helpful and only reducing the environmental factors may not be enough. There are a few difficulties with genetic testing for breeding programs, not only that genetic testing can be expensive (in Israel the price ranges between 130-240€), but also there are differences in the genes that were proven to be connected with CHD between breeds. For this, breeding out is done by phenotypical traits – radiographic screening.

Phenotypical characteristics of CHD is a crucial tool in breeding programs that aim for its incidence reduction. Early hip measurements in puppies, such as the angle of subluxation (AS), angle of reduction (AR), laxity index (LI) and dorsal acetabular rim slope (DARS), can help veterinarians predict the likelihood of a puppy developing CHD. By using these measurements and evaluation into breeding programs, CHD incidence can be reduced. However, it is important to note the values of these measurements vary between breeds. Therefore, developing and applying breed-specific criteria can significantly increase the success of breeding programs in reducing CHD [15].

A recent study by Pinna et al. (2022) examined 632 hip joints from 316 dogs of various breeds. They found that even among dogs classified with normal hips (FCI-A), 31.8% showed mild flattening of the craniolateral acetabular rim, also 58.6% had a slightly divergent joint space in the hip. These findings might be significant when considering selection breeding programs, where the goal is to reduce or eliminate CHD. They suggest that subtle changes associated with CHD may be present even in dogs who are classified with normal hips under current classification systems [29].

4.2. Environmental factors and management

It is important to remember that while a dog may have genetic predisposition for CHD, it does not mean that it will be expressed. Environmental factors can be triggers for CHD; therefore, it is important to recognize those factors and reduce them as much as possible.

Being aware of the environmental factors and applying them to dog breeds with predisposition for CHD can help prevent the progression of the disease.

The Environmental risk factors of CHD [8], [5]:

- high caloric intake (excessive food consumption)
- excess protein and calcium consumption
- rapid growth rate – especially in the first 6 months of life
- unsuitable exercise levels (either excessive or insufficient).

There are other factors that have been associated with CHD development such as body size, season of birth, and in utero endocrine influences. However, it is important to note that these environmental factors do not cause CHD alone, they act as triggers in dogs with genetic predispositions to CHD [8], [5].

According to a study by Kealy et al. (1997), dietary management appears to be a crucial factor in prevention of the effects of CHD. In this study 48 Labrador Retrievers puppies were divided into 2 groups, the first group was fed ad libitum, and the second group had a restricted diet (they were fed 25% less than the first group), over the course of a 5-year period. The study found that the second group (with the restricted diet) had a 38% lower incidence of hip OA by the 5 years of age. The mean body weight of group 1 was 32.5 kg, compared to 22.5 kg in the second group. This study provide evidence that maintenance of lean body condition, by restricted feeding, can be an effective strategy in the reduction of the risk and severity of CHD and associated OA [30]. This study provides evidence that excessive food consumption and high body weight are risk factors of CHD, while restricted diet and lean body weight are protective factors.

5. Prevention strategy in a dog breed in Israel

The Israeli Retriever Club, member of the Israeli Kennel Club, is a registered association that brings together the Retrievers breeds in Israel: Golden Retriever, Labrador Retriever, Flat-Coated Retriever and Nova Scotia Duck Tolling Retriever. This association works in partnership with the FCI as well in order to ensure correct breeding selection.

According to Gali Sokolovski, CEO of the Israeli Retriever Club (personal communication, Oct.15, 2024), the club's objectives are to develop and promote the retriever breeds in the country, provide information related to the club's breeds, assist new dog owners, and initiate and organize dog-related and social activities for club members.

The club's board, active members, and committee members are elected every two years by the club's general assembly. All positions in the club are held on a voluntary basis.

The goal for the Israeli Retriever Club is the maintenance of Retrievers with preservation of each breed's characteristics (external and behavior) and breeding only healthy dogs. To achieve this goal, they go by the guidelines of the FCI for breeding selection. Each individual dog needs to be evaluated with DNA testing and veterinarians, including radiographic screening, which is tailored to the specifics of the breed.

In order to reduce the incidence of CHD, each dog, of the Retriever family, must be evaluated with radiographic screening by three veterinarians, grading by the FCI system (A-E). The scores of these three veterinarians are averaged and is then the official hip score of the dog. Genetic testing is still not available for commercial use, because of the polygenic and complex characteristic of CHD, therefore a careful evaluation with radiographic screening is the most accurate diagnostic method.

Female dogs who are graded A, B, and C are approved for breeding with preference to the dogs with better scores while females graded D or E are denied for breeding. In order for males to be accepted for breeding they must be scored A or B, males with lower scores are denied for breeding. For a female with a C score must get excellent scores in official dog show in order to be approved for breeding. This acts as another selection before breeding, ensuring healthy offsprings.

Dr. Jonathan Shani, B.Sc (Mech. Eng), DVM, Dipl. ECVS, ACVSMR is a veterinary specialist in small animal surgery, his main area of expertise is orthopedic surgery. Working in a veterinary specialty center in Israel.

Chavat Daat (Knowledge Farm), is the biggest private Veterinary Specialty Referral Center in Israel. In March 2007 the Veterinary Specialist Referral Center Knowledge Farm (Chavat Daat) was established at Beit Berl college providing imaging (ultrasound, CT and radiographs), general orthopedic soft tissue services and veterinary oncology services to general veterinary practitioners and their clients. The center employs over 20 board certified specialists and emergency doctors and over 30 qualified veterinary technicians and support staff.

According to Dr. Jonathan Shani (personal communication, Oct.8, 2024) patients with suspected CHD are diagnosed using radiological imaging. For juvenile patients predisposed to CHD, the Barden and Ortolani tests are performed under anesthesia to assess hip laxity and subluxation

Dr. Shani mainly performs total hip replacements for young patients with hip laxity and clinical lameness, for older patients with OA due to CHD, and for patients with traumatic luxation of the hip joint that cannot be successfully reduced to maintain the natural joint. His colleague Dr. Ori Segal, BSc, DVM, Dipl. ECVS, performs Juvenile pubic symphysiodesis in patients younger than 20 weeks old, in order to prevent the progression of CHD.

6. Discussion

Future studies on CHD should focus on improving the breed-specific early evaluation criteria in order to increase the accuracy of prediction and prevention. A study by Pinna et al. (2022) showed deviations from normal hip joints of joints that were classified as FCI-A and FCI-B [29]. This finding can have great significance when considering the persistent high incidence of CHD.

The research by Merca et al. (2020) demonstrates that early hip evaluation can predict the pathological changes of the hip conformation, however the accuracy of these predictions varies across the breeds. Developing more detailed breed-specific models could increase the ability to identify individuals with CHD earlier in life. Furthermore, combining these early physical measurements with genetic markers can increase the accuracy of CHD prediction. By using both phenotypic and genotypic data, researchers may be able to create a model for CHD prediction that account for the complex, multifactorial basis of CHD. Using such approach in breeding programs can help develop more efficient prevention of CHD, allowing a more targeted breeding selection and help reduce CHD significantly across dog breeds [15].

The validation study by Mikkola et al. (2021) provides important insights into the genetics of CHD. The identification of breed-specific and shared genetic markers highlights the need for breed-specific approaches in genetic testing. The discovery of the potential involvement of neddylation pathway in CHD opens new possibilities for research into the molecular mechanisms of this condition [24].

The study by Bruun et al. (2020) on the Dysgen test highlights the significant challenges in developing and applying genetic tests for CHD. Despite the promising results in the Spanish Labrador Retrievers that had high accuracy in CHD prediction, the test failed when applied to Danish dogs and showed no significant correlation with radiographic hip status. This outcome highlights the complexity of CHD genetics and suggests the possibility of significant differences between different geographic or breeding populations of the same breed, complicating the development of reliable universal breed-specific genetic test [28].

7. Conclusions

Canine Hip Dysplasia is a common complex orthopedic condition affecting dogs worldwide, with a higher prevalence in large breed dogs. Both genetic predisposition and environmental factors affect the prevalence of CHD and its progression. The polygenic nature and variable expression across breeds make CHD a challenging subject for both research and clinical management.

The current gold standard for CHD diagnosis remains radiographic screening, combined with systems like the FCI and OFA that provide valuable classification for assessment. However, diagnosing only by phenotypical traits can have inaccuracies and therefore might be one of the causes that CHD remains the most common orthopedic condition. While there is no complete genetic mapping for CHD, using the knowledge of SNPs proven to be related to this condition, in combination with phenotypical findings can potentially offer an earlier diagnosis with higher accuracy and subsequently help decrease CHD prevalence. Breeding programs based on phenotypical traits (using FCI standard) have shown some success, but the integration of genetic screening could significantly increase their success. Moreover, the role of environmental factors cannot be overlooked in CHD prevention and management.

Several areas of CHD need further investigation in the future:

1. Development of breed specific genetic tests for CHD with consideration to the polygenic nature of the condition.
2. Using both phenotypical measurements and genotypic data to create higher accuracy predictive models for CHD.
3. Conduct more research about prevalence in more breeds and in mixed breeds.

While many studies have invested in the understanding and managing of CHD, it remains a challenging condition in veterinary medicine. By combining more genomic research with improved diagnostic techniques and management strategies, it is possible to reduce CHD incidence worldwide.

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