REVIEW

Canine hip dysplasia: Pathogenesis, phenotypic scoring, and genetics

Carmen Peterson
Department of Biology, University of Minnesota Duluth

Abstract

Canine hip dysplasia (CHD) is a painful, incurable disease affecting over 50% of domesticated dogs, with a higher prevalence occurring in purebreds. All canines are born with normal hips, but around week three, development of hip dysplasia begins in dogs with a genetic predisposition to the disorder. Current methods used for diagnosing CHD are based on phenotype, using BVA or OFA scores, and EBVs. These methods are biased and produce false positive and negative results; they also have not reduced the occurrence of CHD because environmental factors of diet and exercise contribute to CHD, along with genetics. Three significant genetic mutations that occur in dogs with hip dysplasia are carbohydrate sulfotransferase 3, fibronectin 1, and fibrillin 2. With the current emergence of genetic research, researchers can develop a method to fix these mutated genes.

INTRODUCTION

In the United States, approximately 70-80 million people own dogs to support their mental, physical, and emotional well being, and because canines provide nurturing, unconditional love to practically everyone (ASPCA 2015, Dotson and Hyatt 2008). Unfortunately, more than 50% of domestic canines are affected, to varying degrees, with a problematic disorder called canine hip dysplasia (CHD) (PennHIP [date unknown]).

Canine hip dysplasia is a heritable, **polygenic** disorder with both environmental and genetic components (Janutta and Distl 2006). CHD causes ailments such as lameness and painful arthritis in dog's hips. These symptoms can cause changes in the dog's personality and behavior, making them irritable and potentially harmful to people. Not only does this make life for the owners and canine(s) emotionally stressful, CHD can be financially stressful as well. Surgeries to help the condition can cost between $1000 and $6000, and will only help relieve pain the dog experiences in his or her hip(s), but will not cure the disease (Zhu et al. 2012).

This review article will discuss how canine hip dysplasia develops, the causes of CHD, methods currently used in diagnosing the disorder, and then will delve into the current expanding genetic research on CHD. Three significant genes will be described, which contribute to the understanding of how examining CHD genetics will help reduce its prevalence.

Polygenic: More than one gene influences the trait
Femoral head: top of the femur (Figure 5)
Acetabulum: Pelvic socket (Figure 5)
Ossification: Bone formation

Corresponding Author:
Carmen Peterson
petersonc743@gmail.com

Development of Normal and Dysplastic Hips

In canines with normal hip development, the **femoral head** is positioned perfectly within the **acetabulum** so that normal **ossification** occurs (Figures 1A, 2, and 3A). All dogs are born with normal hips, but in canines with hip dysplasia development begins appearing around week 3 in the femoral head and pelvic socket regions (Figure 3) (Kealy et al. 1992).

Hip Dysplasia: When the femoral head sits abnormally in the acetabulum, causing luxation (Figures 1B-1F and Figure 4; Wilson et al. 2012)

Luxation: Dislocation top of the femur (Figures 1B-F and 3B)

Articular cartilage: Normally smooth white tissue covering the bone ends, between joints (Figures 1A and Figure 2)

The teres ligament is responsible for holding the femoral head in place during the first month of normal development (Figure 2). In canines with **hip dysplasia**, the teres ligament is too short, so the femoral head does not properly attach and **luxation** occurs after about 2 months of age (Figures 1B-F, 3B-week 9, and Figure 4). At 2-3 months of age in canines with hip dysplasia, the changes of development, compared to normal hip development, when viewed radiographically, are dramatic (Figures 1, 2, 3, and 4). In dogs with CHD, femoral head luxation increases, causing an ossification delay due to the femoral head no longer being able to fit into the acetabulum (Figures 1B-F, 3B, and 4). The **articular cartilage** that surrounds the femoral head is healthy in dogs without CHD (Figures 1A, and 2), but in dogs with CHD, the articular cartilage is worn where it contacts the acetabulum (Figures 1G-H and 4). The hip joint becomes unstable due to the acetabulum and femoral head pulling away from each other and new bone is formed in the acetabulum to make up for the loss of cartilage, causing further luxation (Figures 1B-F, 3B-weeks 9-35, and 4). As the hip becomes dysplastic, the dog experiences discomfort and pain (Riser et al. 1985). CHD is a disease that can affect all breed types, with a higher frequency occurring in purebred canines, and does not discriminate against a specific breed size.

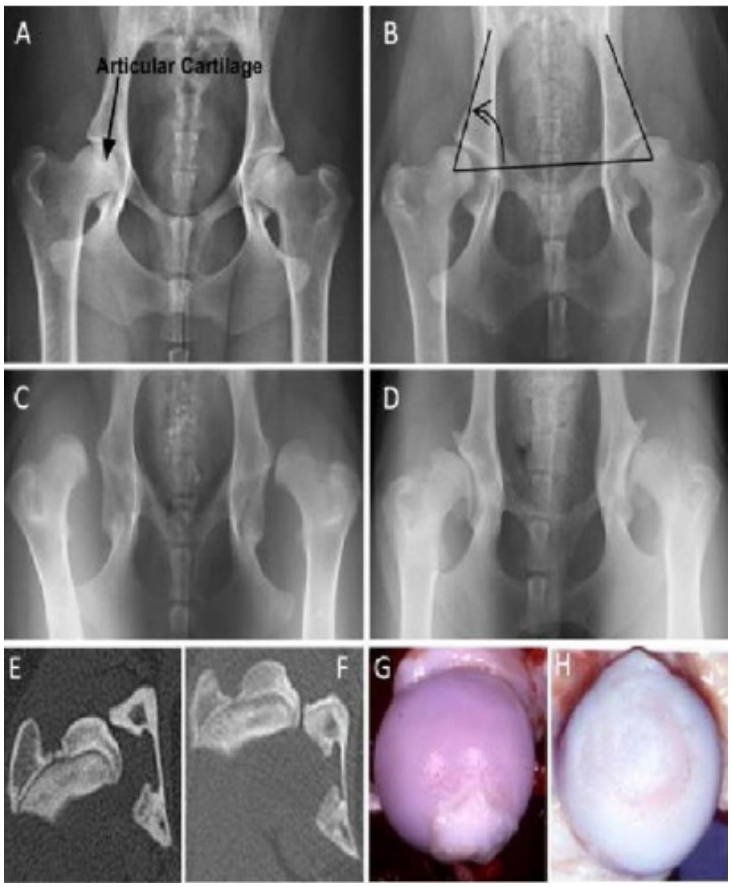


Figure 1: A. normal hip configuration (radiograph) B. canine with moderate hip dysplasia (radiograph) C. canine with luxation demonstrating severe hip dysplasia (radiograph) D. canine with osteoarthritis as a result of hip dysplasia (radiograph) E. canine hip with moderate hip dysplasia due to subluxation (CT image) F. canine with severe hip dysplasia from complete luxation (CT image) G. femoral head that is moderately affected with CHD and early effects of osteoarthritis (photograph) H. femoral head with severe CHD due to articular cartilage erosion and ligament degradation (photograph). (Adapted from Zhou et al. 2010, Plos One, free access journal).

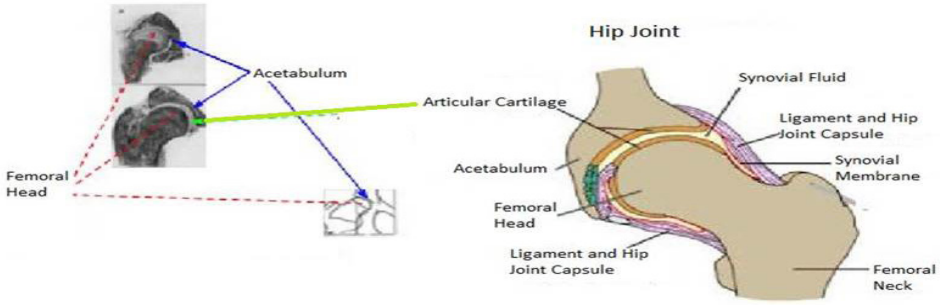


Figure 2: Anatomy of normal hip development. Notice how the femoral head sits into the acetabulum with healthy articular cartilage surrounding the femoral head. (Adapted from Riser et al. 1985 and Healthbase 2017)

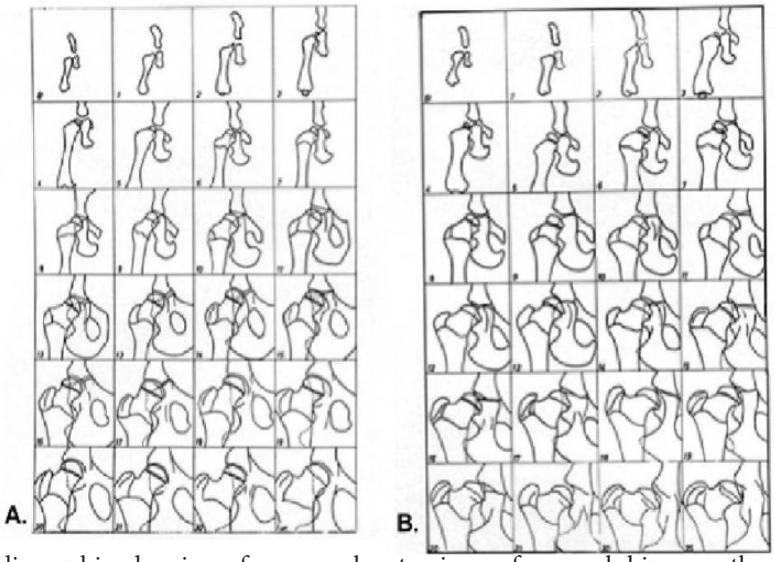


Figure 3: A. Radiographic drawings from overlay tracings of normal hip growth and development from birth to one year old. B. Radiographic drawings from overlay tracings of dysplastic hip growth and development from birth to one year old; notice that by week 3 the femoral head and pelvic socket already do not have normal alignment. (Adapted from Riser et al. 1985)

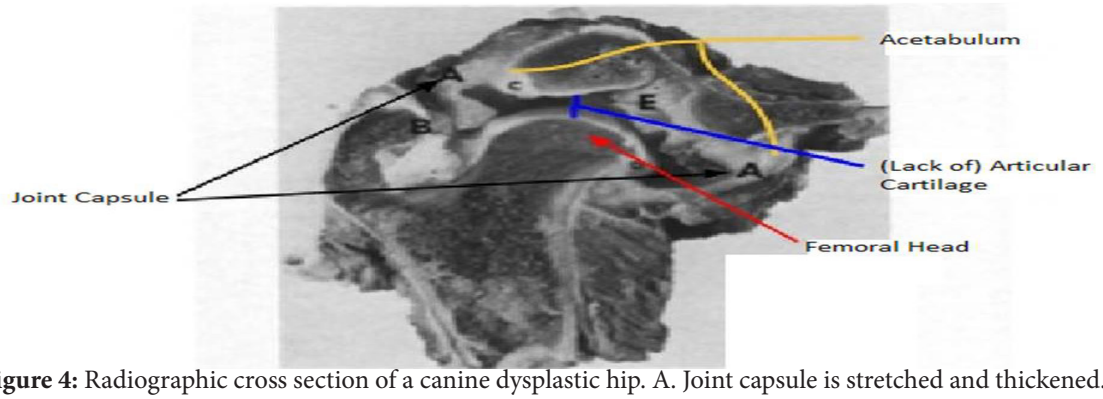


Figure 4: Radiographic cross section of a canine dysplastic hip. A. Joint capsule is stretched and thickened. B. dorsal bending occurs around femoral neck C. lagging development of acetabular rim causes change in shape D. Ventral side of femoral head begins to slope E. Trauma of teres ligament. (Adapted from Riser et al. 1985).

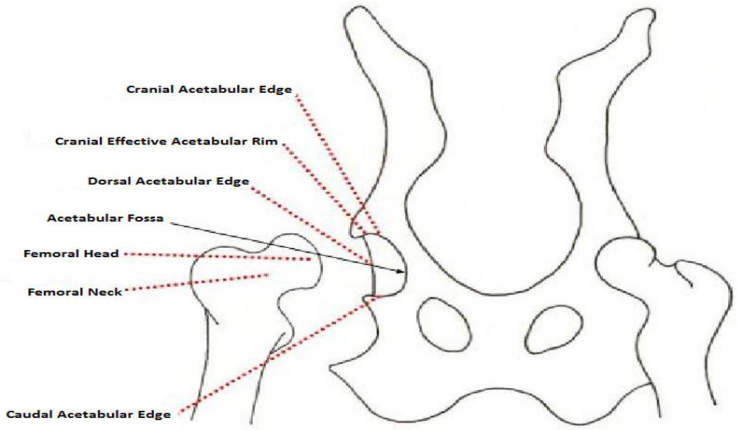


Figure 5: Anatomy of canine hip. Labeled are 7 out of 9 anatomical areas of the hip that are examined when scoring based on either the BVA or OFA standard. The areas scored are: the cranial acetabular edge, dorsal acetabular edge, cranial effective acetabular rim, acetabular fossa, caudal acetabular edge, femoral head and neck exostosis (benign bone growths), Norberg Angle (the displacement between the cranial femoral head and acetabulum), and subluxation (partial dislocation, in this case around the femoral head) (Wilson et al. 2013, Lewis et al. 2010; Figure adapted from Lewis et al. 2010)

Types of Canines Affected

CHD has a higher prevalence in purebred canines due to the lack of genetic diversity (Baker Institute for Animal Health 2005, Sanchez-Molano 2014a). Purebred means that the parents and ancestors are of the same breed, and are registered members of the American Kennel Club or United Kennel Club (Dog Guide 2017). Canines are recognized as being either purebred or mixed breed and are categorized further based on size. Mixed breed dogs are offspring of 2 or more different breeds, with one, or both parents not being registered purebreds (Dog Guide 2017), and sizes are classified as large, medium, and small. All breed sizes can be affected by CHD, because any dog that gains excess weight too fast tends to have irregular hip development. Veterinarians currently use phenotypic scoring methods to diagnose CHD.

BVA: British Veterinary Association

OFA: Orthopedic Foundation for Animals

EBV: estimated breeding value

Methods for Diagnosing CHD

In order to diagnose a dog with hip dysplasia, veterinarians take radiographic images of the canine's pelvic region. These images are typically taken after the dog has been exhibiting discomfort and pain in their hip(s). After the radiographs are taken, veterinarians or radiologists then grade the hip(s) using either the **BVA** or **OFA** scoring system. The BVA and OFA rating standards produce false positive and negative results, so another method, **EBV**, was added. However, EBVs are biased, so neither the BVA or OFA standard, or the EBV, have reduced the prevalence of CHD.

BVA or OFA Standards

Veterinarians score canine hips for the development of CHD using one of two common rating standards, the BVA or OFA. Both standards generate a score by examining and rating nine anatomical areas of an individual canine's hip. A higher score indicates a higher susceptibility to CHD (Wilson et al. 2013, Lewis et al. 2010, Sanchez-Molano et al. 2014b).

Figure 5 shows a diagram and a list of these nine anatomical areas that contribute to the BVA or OFA score. To improve the accuracy of BVA and OFA scores, researchers have added two statistical components that are comprised in an EBV.

Use of Estimated Breeding Values to Predict CHD

Mixed-model: Used in statistics as a generalized linear model that contains random and fixed effects

An EBV is a **mixed-model** that calculates the dog's probability for breeding a certain trait (Wilson et al. 2013). The EBV is an important tool for breeders, researchers, and veterinarians for predicting the statistical prevalence of CHD. EBVs include the canine's BVA or OFA score, along with pedigree information, and environmental effects. The additional information included in an EBV improves the predictive score. Just like with the BVA or OFA scores, a higher EBV implicates a higher risk of that particular individual developing CHD (Leighton 2003; Wilson et al. 2011). EBVs use a mixed-model that lacks a universal method, and can contain false positives and negatives from BVA or OFA scores, which cause biased results.

Problems with Current Diagnostic Methods

The BVA or OFA score alone is a poor predictor for knowing the canine's risk of developing CHD; the main reason being that the scores are taken after the dog's birth, and do not involve looking at the parent's genetics to see if they are passing viable CHD genes on to their offspring. Also, BVA and OFA scores can produce false positive and negative results. When adding the BVA or OFA scores together with pedigree information and environmental effects to comprise the EBV, researchers believed this would decrease the prevalence of CHD, however EBVs have only become biased.

False Positives and Negatives

Canine hip scores are evaluated compared to a non-breed-specific threshold value, and false positives or negatives can occur when using the BVA or OFA standards (Culp et al. 2006). The misdiagnosis that occurs with the false positives or negatives can lead to improper breeding choices and the recurrence of CHD in the population. When false positives occur, canines are mistakenly eliminated from breeding and passing their healthy genes onto their offspring. When false negatives occur, canines with CHD promoting genes are allowed to pass the diseased genes on to their offspring, causing canines to have a higher probability of developing CHD (Culp et al. 2006). Along with the false results of BVA or OFA scores, EBVs are biased.

Biases of EBVs

EBVs lack a universal equation, or set of equations, and typically the data collected for submission into the EBV is voluntary. Veterinarians or breeders will often only submit favorable EBVs that have been taken from radiographs of offspring chosen to be breeding candidates (Wilson et al. 2013, Zhang et al. 2009). Other dogs in the pedigree may be ignored and therefore the risk of CHD is underreported for the dog. With the false positive and negatives that occur using BVA or OFA scores, along with the biases of EBVs, together these demonstrate how previous techniques have failed at diagnosing CHD. This disease is difficult to diagnose due to its two major causes: environment and genetics.

Causes of CHD

Environmental and genetic factors play a key role in CHD. The environment affects the canine because the amount of exercise and diet type are important factors for a healthy dog. Genetics play the biggest role in the development of CHD because mutated genes are passed on to the offspring due to lack of knowledge about the genes that affect CHD. Emerging genetic research can one day decrease the prevalence of CHD.

Environmental factors: Abiotic and/ or biotic factors that influence an organism

ad libitum: Unlimited

Prolifeation: Rapid reproduction of cells

Palpable: Ability to be touched or felt

Proteoglycans: important proteins that are found in the extracellular matrix of connective tissue (Yanagishita 1993, Hermanns et al. 2008)

Environmental Factors

The **environmental factors** that contribute to CHD include the level of exercise and diet, which both supplement the dog's body weight and muscle mass. Kealy et al. found that only 7 out of 24 "limit-fed" Labrador Retrievers were diagnosed with hip dysplasia, while 16 out of 24 canines with an "**ad libitum**" diet were diagnosed with hip dysplasia (1992). When a dog has extra weight, many instability issues occur: **proliferation** of the dorsal acetabular rim, atrophy of local muscles, stretching of ligaments in the femoral head, cartilage degeneration, and thickening of the joint capsule and femoral neck (Figure 4) (Fries and Remedios 1995). A canine with proper diet and exercise should have a slender figure, with **palpable**, but not visible ribs. Environmental effects play a significant role in CHD, but the major contributing factor to CHD is genetics.

Genetic Factors

A dog's genetics also play a complicated role, because CHD is an inherited disease. Heritability is the amount of a trait that is passed on from parents to offspring through their genes. The heritable relationship of CHD between parents and offspring means that the expression of certain genes determines how the hips develop, which includes the size, shape, anatomical relationships, and musculature. Fries and Remedios found that 85% of offspring have CHD when both parents have dysplastic hips, 52% of offspring if one parent has dysplastic hips, and 37.5% of offspring if both parents have normal hips (1995). Fries and Remedios' study demonstrates how important genetic diversity is in preventing the spread of hip dysplasia in future canines (1995). Emerging genetic research will be beneficial in decreasing the prevalence of CHD because researchers can identify and target mutated genes.

Genotype Research

Understanding more about the genetic root of CHD will help veterinarians and breeders make better breeding selections, and decrease the prevalence of canine hip dysplasia. Researchers have found a high correlation between genetics and hip scores (from the BVA and OFA values), which suggests that there is a genetic basis for predisposition to CHD (Lewis et al. 2010). In current literature about CHD, three genes are prominent: carbohydrate sulfotransferase 3 (CHST3), fibronectin 1, and fibrillin 2 (FBN2).

CHST3

Carbohydrate sulfotransferase 3 (CHST3) is a protein coding gene for the enzyme sulfotransferase that catalyzes synthesis of the **proteoglycan**, chondroitin sulfate, which provides structure in the extracellular matrix of joint cartilage (GeneCards 2016, Bartolome

et al. 2015). In canines with hip dysplasia, CHST3 has a missense mutation that occurs in exon 3, where a substitution of glycine appears with arginine (Tanteles et al. 2013). This mutation causes deficiencies in the formation of joint cartilage leading to hip malformation.

Fibronectin 1

A CHD-associated **SNP** was found near fibronectin 1 on chromosome 37 (Pfahler and Distl 2012). Fibronectin 1 is an important **glycoprotein** that plays a role in the extracellular matrix of cartilage. In canines with normal hips, there is a small amount of fibronectin in the cartilage, while canines with dysplastic hips have large amounts of this glycoprotein (Wurster and Lust 1982). The accumulation of fibronectin in dysplastic hips may be due to the loss of extracellular matrix in the joint, which causes a build-up of this glycoprotein in the cartilage (Wurster and Lust 1982)

SNP: Single nucleotide polymorphism

Glycoproteins: Polypeptide chains with attached carbohydrate groups

Fibrillin 2

A crucial structural gene that is significant for the framework of canine tendons is fibrillin 2 (FBN2), which is found on chromosome 11 (Zhou et al. 2010, Friedenberg et al. 2011, Lavrijsen et al. 2014). FBN2 plays a vital structural role in elastic tissue of the extracellular matrix present in joints, especially in the tendons (Boregowda et al. 2008, Zhu et al. 2012). In canines with normal hips, FBN2 assembles to become a framework of elastic fibers and provides a place for growth factors to stimulate cellular growth (Boregowda et al. 2008). In canines with dysplastic hips there is a deletion of the fibrillin 2 gene on chromosome 11 (Zhu et al. 2012). The deletion of this gene causes alterations in the connective tissue around the joint, leading to hip malformation (Zhu et al. 2012, Boregowda et al. 2008).

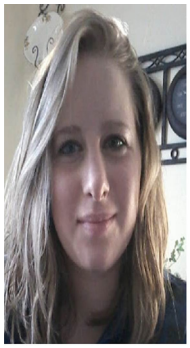
CONCLUSION

Canine hip dysplasia is a painful, heritable, and polygenic disease that causes hip malformation due to improper alignment of the acetabulum and femoral head. Development of CHD begins around week 3 in predisposed canines. The current phenotypic methods of using BVA or OFA scores, and EBVs, have been unsuccessful in decreasing the occurrence of CHD. With over half the population of domesticated dog breeds being affected by CHD, new methods for abating this disorder need to be done. Carbohydrate sulfotransferase 3, fibronectin 1, and fibrillin 2 are three mutated genes that appear across research about CHD. By looking at the genetic components of CHD researchers can conceivably find a way to fix these mutations that occur. For breeders, dog DNA tests are available to potentially identify the mutated genes before breeding, and select other canines without these genes to breed. Using the DNA tests, breeders can also add genetic diversity to the pedigree by breeding dogs with diverse genetic makeups. Alongside the genetic components, environmental factors also affect CHD, so dog owners need to have the proper knowledge about their canine(s) to ensure they are feeding them a proper diet and giving them the appropriate amount of exercise.

Acknowledgments

I express an extreme amount of gratitude to be honored with this splendid experience of being part of DJUB. I thank all of the anonymous peer-reviewers who have provided me with great feedback to polish my review article for publication. I especially would like to

thank Dr. Judi Roux, Dr. Shannon Stevenson, and Ms. Tami Rahkola for reaching out to me and considering my manuscript for publication in DJUB. I am really grateful for all of the help, support, guidance, insight, and wisdom I received from all of my family and friends as well. Thank you all!



Biography

Carmen Peterson is a student pursuing two degrees, a B. S. in Biology and a B. A. in English. She is aspiring a career in the Veterinary field. In her free time she enjoys spending time with nature, hiking, reading, biking, camping, making fun bracelets, and volunteering at local Humane Societies.

References

ASPCA (American Society for the Prevention of Cruelty to Animals). 2015. Pet Statistics [Internet]. [cited 15 February 2017.] Available from https://www.aspca.org/animal-homelessness/shelter-intake-and-surrender/pet-statistics

Baker Institute for Animal Health. 2005. Diagnosis and genetics of canine hip dysplasia. Cornell University: College of Veterinary Medicine 11(5):1-10.

Bartolome N, Segarra S, Artieda M, Francino O, Sanchez E, Szczypiorska M, Casellas J, Tejedor D, Cerdeira J, Martinez A, et al. 2015. A genetic predictive model for canine hip dysplasia: Integration of genome wide association study (GWAS) and candidate gene approaches. Plos One. 10(4):e0122558

Boregowda R, Paul E, White J, Ritty TM. 2008. Bone and soft connective tissue alterations result from loss of fibrillin-2 expression. Matrix Biol. 27(8):661-666

Culp WT, Kapatkin AS, Gregor TP, Powers MY, McKelvie PJ, Smith GK. 2006. Evaluation of the Norberg angle threshold: a comparison of Norberg angle and distraction index as measures of coxofemoral degenerative joint disease susceptibility in seven breeds of dogs. Vet Surg. 35(5):453–459

Dog Guide. 2017. What's the difference between purebred, mixed breed, and hybrid dogs? [Internet]. The Fun Times Guide; [cited 05 April 2017]. Available from https://dogs.thefuntimesguide.com/hybrid_dog/

Dotson MJ, Hyatt EM. 2008. Understanding dog-human companionship. J Bus Res. 61(5):457-466

Friedenberg SG, Zhu L, Zhang Z, van den Berg Foels W, Schweitzer PA, Wang W, Fisher PJ, Dykes NL, Corey E, Vernier-Singer M, et al. 2011. Evaluation of a fibrillin 2 gene haplotype associated with hip dysplasia and incipient osteoarthritis in dogs. Am J Vet Res. 72(4):530-540

Fries CL, Remedios AM. 1995. Pathogenesis and diagnosis of canine hip dysplasia: a review. Can Vet J. 36:494-502

GeneCards. 2016. Carbohydrate (Chondroitin 6) Sulfotransferase 3 [Internet]. Weizmann Institute of Science; [cited 28 January 2017]. Available from http://www.genecards.org/cgi-bin/carddisp.pl?gene=CHST3

Healthbase. 2017. Neck Capsule Preservation (NCP) approach in Birmingham hip resurfacing [Internet]. Healthbase Online Inc; [cited 22 March 2017]. Available from http://www.healthbase.com/resources/orthopedics/hip-resurfacing-surgery/neck-capsule-preservation-ncp-approach-birmingham-hip-resurfacing-vijay-bose-india-medical-tourism.html

Hermanns P, Unger S, Rossi A, Perez-Aytes A, Cortina H, Bonafé L, Boccone L, Setzu V, Dutoit M, Sangiorgi L, et al. 2008. Congenital joint dislocations caused by carbohydrate sulfotransferase 3 deficiency in recessive Larsen syndrome and humero-spinal dysostosis. Am J Hum Genet. 82(6):1368–1374.

Janutta V, Distl O. 2006. Inheritance of canine hip dysplasia: review of estimation methods and of heritability estimates and prospects on further developments. Dtsch Tierarztl Wochenschr. 113(1):6-12

Kealy RD, Olsson SE, Monti KL, Lawler DF, Biery DN, Helms RW, Lust G, Smith GK. 1992. Effects of limited food consumption on the incidence of hip dysplasia in growing dogs. J Am Vet Med Assoc. 201(6):857-863
Lavrijsen ICM, Leegwater PAJ, Martin AJ, Harris SJ, Tryfonidou MA, Heuven HCM, Hazewinkel HAW. 2014. Genome wide analysis indicates genes for basement membrane and cartilage matrix proteins as candidates for hip dysplasia in Labrador Retrievers. Plos One. 9(1):e87735

Leighton EA. 2003. How to use estimated breeding values to genetically improve dog guides. Paper presented at: Meeting of the "Original Group" 2003. The Seeing Eye, Inc., P.O. Box 375, Morristown, New Jersey.

Lewis TW, Woolliams JA, Blott SC. 2010. Genetic evaluation of the nine component features of hip score in UK Labrador Retrievers. Plos One. 5(10):e13610

PennHIP. [date unknown]. Introduction to Canine Hip Dysplasia [Internet]. Antech Diagnostics, Inc. [cited 26 April 2017]. Available from http://info.antechimagingservices.com/ pennhip/navigation/hipDysplasia/ introduction.html

Pfahler S, Distl O. 2012. Identification of quantitative trait loci for canine hip dysplasia and canine elbow dysplasia in Bernese Mountain dogs. Plos One. 7(11):e49782

Riser WH, Rhodes WH, Newton CD. 1985. Hip dysplasia. Textbook of Small Animal Orthopaedics. Chapter 83.

Sanchez-Molano E, Woolliams JA, Blott SC, Wiener P. 2014a. Assessing the impact of genomic selection against hip dysplasia in the Labrador retriever dog. J Anim Breed Genet 131:134-145

Sanchez-Molano E, Woolliams JA, Pong-Wong R, Clements DN, Blott SC, Wiener P. 2014b. Quantitative trait loci mapping for canine hip dysplasia and its related traits in UK Labrador Retrievers. BMC Genom. 15:833

Tanteles GA, Dixit A, Dhar S, Suri M. 2013. Two Somali half-siblings with CHST3-related chondrodysplasia illustrating the phenotypic spectrum and intrafamilial variability. Am J Med Genet. 161(10):2588-2593

Wurster NB, Lust G. 1982. Fibronectin in osteoarthritic canine articular cartilage. Biochem Biophys Res Commun. 109(4):1094-1101

Wilson B, Nicholas FW, Thomson PC. 2011. Selection against canine hip dysplasia: Success or failure? Vet J. 189:160-168

Wilson BJ, Nichols FW, James JW, Wade CM, Tammen I, Raadsma HW, Castle K, Thomson PC. 2012. Heritability and phenotypic variation of canine hip dysplasia radiographic traits in cohort of Australian German Shepherd dogs. Plos One 7(6):e39620

Wilson BJ, Nicholas FW, James JW, Wade CM, Thomson PC. 2013. Estimated breeding values for canine hip dysplasia radiographic traits in a cohort of Australian German Shepherd dogs. Plos One. 8(10):e77470

Yanagishita M. 1993. Function of proteoglycans in the extracellular matrix. Acta Pathol Jpn. 43(6):283-293.

Zhang Z, Zhu L, Sandler J, Friedenberg SS, Egelhoff J, Williams AJ, Dykes NL, Hornbuckle W, Krotscheck U, Moise NS, et al. 2009. Estimation of heritabilities, genetic correlations, and breeding values of four traits that collectively define hip dysplasia in dogs. Am J Vet Res. 70(4):483-491

Zhou Z, Sheng X, Zhang Z, Zhao K, Zhu L, Guo G, Friedenberg SG, Hunter LS, Vandenberg-Foels WS, Hornbuckle WE, et al. 2010. Differential genetic regulation of canine hip dysplasia and osteoarthritis. Plos One. 5(10):e13219

Zhu L, Chen S, Jiang Z, Zhang Z, Ku HC, Li X, McCann M, Harris S, Lust G, Jones P, Todhunter R. 2012. Identification of quantitative trait loci for canine hip dysplasia by two sequential multipoint linkage analyses. J Appl Statistics. 39(8):1719-1731