Femoral Arthritis and Proximal Femoral Morphology in Portuguese Water Dog Femora Demonstrate Avenues for Establishing Etiological Relationships via Genetic Analyses

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INTRODUCTION: Osteoarthritis of the hip is a common problem among humans, where studies have estimated it affects 3% of adults over the age of 30 [1]. In canines it is estimated that 20% of adults have some type of osteoarthritis [2]. Age is a determinant risk factor for arthritis [1], but cannot account for all cases, especially those occurring in the young population. Misalignment of the head-neck junction has been proposed to induce cartilage damage via femoroacetabular impingement. While there have been studies showing femoroacetabular impingement to be responsible for early onset osteoarthritis [3], this relationship cannot be deemed to be causal in view of available data [4]. Because the cervico-diaphyseal angle, lateral head offset, and anteversion angle of the femoral head determine the alignment of the hip, previous studies have sought to elucidate if anatomical variances in these measurements contribute to the development of arthritis [1,3,5]. These studies lacked the large sample size and genetic information that is present in our sample of Portuguese Water Dog (PWD) femora. PWD femora were obtained through the Georgie Project [6,7]. These PWDs were chosen because they have a pedigree that can be traced back to 31 founders through 24 generations. The sex, weight, and age at time of death are known for all the dogs in our study. We chose this cohort due to the availability of genetic data on the PWDs. The purpose of our study was to analyze PWD proximal femur morphology to better understand the development of osteoarthritis. We focused this analysis particularly on parameters most related to the geometry of the hip: cervico-diaphyseal (CD) angle, lateral head offset (Lho), and femoral head anteversion (AV) angle. We sought to answer these questions with our large sample of PWD femora: (1) Does CD angle change with age in either sex? (2) Does Lho change with age in either sex? (3) Does AV angle change with age in either sex? (4) Does the presence of head arthritis (Head.A) change with age in either sex? (5) Do changes in CD, Lho, or AV angle alter the occurrence of Head.A?
METHODS: With IACUC approval, PWD carcasses were autopsied for various organ pathologies in prior studies [6,7] (n=314, age range 2-18 years, Male: n=130, Female: n=184, soft tissue manually removed). The right femur from each dog was examined for the presence of femoral head and condylar arthritis. The rating of Head.A was in accordance with the methods of Dennis [9] (where 0 is normal and arthritis is progressively worse from 1, 2, …5 and condylar arthritis (Con.A) was considered normal=0, mild=1, moderate=2, severe=3. Proximal geometric measurements included AV and CD angles, and length of femoral head offset (Lho) [8]. A myriad of additional parameters were analyzed, including: polar moment of inertia (Zpol), polar moment of inertia/biomechanical length (Zpol.Lbio), second minimum moment of area (Imin), second maximum moment of area (Imax), polar moment of inertia/total length (Zpol.Ltot), total area/total length (T.Ar.Ltot), total area/biomechanical length (T.Ar.Lbio), cortical area at 50% shaft location (CA.1), anterior bow max raw data (AB.Max), anterior bow index (AB.index), anterior bow max/biomechanical length (ABmax.Lbio), isthmus width (Isth.wd) (i.e., narrowest medial-lateral dimension of the medullary canal), total length (L.total), biomechanical length (L.bio), total length/isthmus width (L.T.wd), longitudinal axis of the diaphysis (Lhd), longitudinal axis of the diaphysis/biomechanical length (Lhs.Lbio), lateral head offset/biomechanical length (Lho.Lbio), distance femoral head center to greater trochanter (Lht), distance femoral head center to greater trochanter/biomechanical length (Lht.Lbio), cervico-diaphyseal angle (C.D.ang), second maximum moment of area/second minimum moment of area (Imax.Imin), second maximum moment of area/second minimum moment of area/biomechanical length (Imax.Imin.Lbio), percent length anterior bow max (pL.ABmax), percent length anterior bow max/biomechanical length (X.ABmax.Lbio), distance to isthmus from 50% shaft location (Distance.to.Isthmus), robustness (CA.TA), robustness/biomechanical length (CA.TA.Lbio), robustness/total length (CA.TA.Ltot), canal flare index (CFI). All statistics were estimated using custom scripts in R(1) (http://www.R-project.org/). Pearson correlation coefficients were estimated using the 'cor' function, robust line fitting was done with the 'rlm' function. The significance of the sex difference was estimated using a two-sided, unpaired, unequal variance T test (the 't.test' function) (* $p < 0.05$; ** < 0.01; *** < 0.001). Correlations between all traits were tested. Additional detailed genetic analyses are in progress.
RESULTS: AV and CD angles are not correlated and are independent of age and sex with no significant difference between males and females: AV angle in males = 13.5˚(+/- 6.3˚, SD); in females = 13.2˚ (+/- 5.4˚, SD) (p=0.7). CD angle in males = 125.7˚ (+/- 9.7˚, SD); in females = 125.6˚ (+/- 9.4˚, SD) (p=0.9). The lack of a relationship with age and sex can be visualized for CD angle by the regression plot in **Fig. 1** [all bones, r = -0.01, p = 0.9, males vs age (r = 0.17, p = 0.5), females vs age (r = -0.13, p = 0.5)]. Lho was independent of age, but significantly different between males and females. Lho in males = 14.9 (+/- 2.8, SD); in females = 14.1 (+/-2.1, SD) (p = 0.004), which reflects differences in bone size. Head.A was found to be independent of sex (males = 0.7 +/- 1.4, females = 0.7 +/- 1.5) (p = 0.9) with a small, but significant, increase with age in females: Head.A in males vs age ($r < 0.01$, p = 0.5) and females vs age (r = 0.03, p = 0.003). This increase in females with age can be seen in **Fig. 2**. Con.A was 0.3 (+/-0.8, SD) in males and 0.1 (+/-0.5) in females (p = 0.02). Correlation analysis shows a negative relationship between CD angle and Head.A (-0.4) (**Fig. 3**).
DISCUSSION: Our results do not differ from those of Reikerås and Høiseth in humans where CD angle was found to be of no importance in the pathogenesis of idiopathic osteoarthritis of the hip due to no difference being found between sexes or disease state [5]. Our data does show a significant negative relationship between CD angle and Head.A. It is important to note that this finding is likely not causal because arthritis leads to reduction of head sphericity that leads to reduced CD angle. But the contribution of CD angle in our PWD cohort warrants additional study for potential genetic influences, especially to determine influences when multiple traits are considered in the emergence and progression of Head.A. While there was no difference in Head.A between males and females, there was an increased rate of Head.A in females with age. Lho was found to be significantly greater in males, and males were also found to have significantly less Head.A with age. Additional analyses are needed to determine if there is a genetic basis for these sex-related differences and if a protective relationship might exist between Lho and Head.A or if this finding is simply related to bone size. Additional detailed genetic analysis is now underway in our lab. In line with the findings of Weinberg et al. in humans, our findings suggest that AV has no significant bearing on the development of Head.A or Con.A, and that an increased AV angle does not suggest a need to preemptively operate [10]. However, there are conflicting findings in the literature regarding the influence of proximal femoral morphology and emergence and progression of arthritis [1,5], and the role that the canine model has in helping elucidate these relationships in humans is not well established. Our large sample of PWD femora and the genetic data available from these animals will help to clarify these issues in the canine hip for potential translation to the human hip.
SIGNIFICANCE/CLINICAL RELEVANCE: Data from our study will be useful in understanding the etiology of osteoarthritis in canines and could be applicable to the etiology of osteoarthritis in humans.
REFERENCES: 1. Egea et al. (2014) Clinical Biomechanics 29: 444- ; **2.** Malek et al. (2012) BMC Veterinary Research 8:185- ; **3.** Duart et al. (2008) Rev. Esp. Cir. Ortop. Traumatol 52:71- ; **4.** Hack et al. (2010) J. Bone Joint Surg. Am. 92:2436- ; **5.** Reikerås and Høiseth. (1982) Acta Orthop. Scand. 53:781- ; **6.** Chase et al. (2011) Age 33:461- ; **7.** Chase et al. (2002) PNAS 99:9930- ; **8.** Kuo et al. (1998) J. Biomed. Mat. Res., 40, 475- ; **9.** Dennis. (2012) In Practice 34:178- ; **10.** Weinberg et al. (2017) J. Pediatr. Orthop. 37: 120-

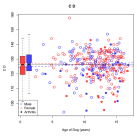
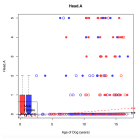


Figure 1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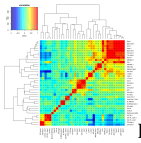
Figure 3