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The genetic epidemiology of joint shape and the development of osteoarthritis

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Overview

Congruent, low-friction relative movement between the articulating elements of a synovial joint is an essential pre-requisite for sustained, efficient, function. Where disorders of joint formation or maintenance exist, mechanical overloading and osteoarthritis (OA) follow. The heritable component of OA accounts for ~50% of susceptible risk. Although almost 100 genetic risk loci for OA have now been identified, and the epidemiological relationship between joint development, joint shape and osteoarthritis is well established, we still have only a limited understanding of the contribution that genetic variation makes to joint shape and how this modulates OA risk. In this article, a brief overview of synovial joint development and its genetic regulation is followed by a review of current knowledge on the genetic epidemiology of established joint shape disorders and common shape variation. A summary of current genetic epidemiology of OA is also given, together with current evidence on the genetic overlap between shape variation and OA. Finally, the established genetic risk loci for both joint shape and osteoarthritis are discussed.

Introduction

Osteoarthritis (OA) is a disorder involving movable joints characterized by cell stress and extracellular matrix damage leading to cartilage degradation, bone remodelling, osteophyte formation, joint inflammation and loss of normal joint function that manifests clinically with pain, deformity, and disability <https://www.oarsi.org/education/oarsi-resources/oarsi-white-paper-oa-serious-disease>. Approximately 240 million people (3.3% of the world's population) live with OA [1]. Between 1990 and 2013 osteoarthritis was responsible for a 75% increase in years living with disability to 13 million [2], behind only diabetes (135%) and dementia (84%) in increasing prevalence. This reduced physical activity results in an increased all-cause mortality for OA sufferers versus the general population (standardised mortality ratio 1.55, 95% confidence interval 1.41 to 1.70) [3], largely attributable to an excess cardiovascular risk. In 2003, OA accounted for 1.2% of United States domestic product (\$128billion, direct costs \$80Billion and loss of earnings \$47Billion) [4]. By 2013, this figure had increased to \$304Billion [5].

The epidemiological risk factors for OA are well-established and include older age, female sex, obesity, joint injury, bone morphology and family history. The heritability of OA has been estimated in studies of monozygotic versus dizygotic twins to range between 40% (knee) and 60% (hip) [6, 7], and follows a non-Mendelian pattern consistent with the common, complex nature of the disease. The interaction between environmental and heritable risk factors for OA also differs with age, between men and women, and with body mass index [8]. In recent years it has become more

1 widely-appreciated that underlying joint shape is a strong risk factor for OA. This realisation has led
2 to an explosion in the use of surgical interventions designed to restore the joint to a more
3 anatomically normal shape and improve mechanical symptoms [9-11]. Only time will establish
4 whether such interventions alter the natural history of OA. In this article, we provide a brief
5 overview of the morphology and development of synovial joints, review the genetic epidemiology of
6 joint shape as it relates to OA genetic epidemiology, and consider to what extent this heritable
7 component is shared.
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11 **What is a synovial joint?**

13 Synovial joints, characterised by a fluid-filled synovial space between the bones, are the most
14 flexible type of joint in the body, allowing movement between the bone ends in up to 6 degrees of
15 freedom and across an arc of movement of up to 140 degrees. Synovial joints are the most common
16 type of joint, and allow great facility in both the range and type of movement from repetitive,
17 weight-bearing activity through to intricate, fine motor functions. Such freedom of movement and
18 resilience requires exquisite design. All synovial joints comprise subchondral bone that is lined by
19 hyaline cartilage and enclosed by a strong fibrous capsule that is lined by synovial tissue. The outer
20 fibrous capsule is reinforced by ligaments that act as primary stabilisers of the joint. The joint cavity
21 is filled with lubricating synovial fluid that is synthesised by the synovial membrane and hyaline
22 cartilage, allowing low friction motion between the joint elements. The joint cavity may also contain
23 fibrocartilage extensions of the capsule that function to spread load more evenly within the joint and
24 act as a secondary stabiliser (knee menisci and hip labrum). Further stabilisation of the joint is
25 provided by accessory ligaments that may be separate to, or fused with, the capsule.
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31 Synovial joints perform a variety of movements, necessitating variation on the same basic design.
32 These include pivot joints that allow rotation (upper cervical vertebra), hinge joints that allow
33 movement in only 1 plane but can allow transfer of large forces to create great power (knee, elbow),
34 saddle joints that allow fine multidirectional movement (small joints of the hand), plane joints that
35 allow limited sliding motion whilst resisting large forces (midfoot), condyloid joints that allow
36 complex composite movement (wrist), and ball and socket joints that can rotate and flex almost
37 freely in any direction whilst maintaining great stability (shoulder, hip).
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43 **An overview of synovial joint development**

44 Despite the heterogeneity of synovial joint morphology, common signalling pathways underpin their
45 development. In this section, we give a brief overview of the process, although dedicated reviews of
46 this topic can be found elsewhere.[12, 13] Bones and joints develop in mesoderm, comprising
47 mesenchymal cells that have the ability to differentiate into fibroblasts, chondroblasts or osteoblasts
48 and the blood vessels and connective tissues of the limb. Synovial joint formation begins at
49 approximately week 7 of embryogenesis as interzonal mesenchyme between the developing bones
50 [14]. Figure 1 shows joint development from mouse data, but the same stages are followed in
51 humans. The outer layers of the interzone form the long bone epiphyses through endochondral
52 ossification [15], whilst the inner layer differentiates into the articular surfaces. Removal of the
53 interzonal mesenchyme during embryonic development results in fusion of the adjacent developing
54 bones [16].
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1 At the molecular level, the appearance of the interzone is accompanied by a decrease in type II
2 collagen expression [17], and an increase in growth differentiating factor 5 (GDF5) and bone
3 morphogenetic protein 2 (BMP2) expression. GDF5, a member of the transforming growth factor
4 beta superfamily [18], is a key early marker of interzone development and segmentation of skeletal
5 elements [19, 20]. *Gdf5* knockout results in failure of synovial joint development in mice [20]. Whilst
6 GDF5 is an essential requirement for joint development, it is not specific to synovial joints, and its
7 over-expression also results in failure of joint formation, increase in size of the skeletal elements and
8 over-proliferation of epiphyseal cartilage [21].
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10 Interzone expression gradients of BMPs and their inhibitors Noggin and Chordin also regulate
11 appropriate synovial joint development [22, 23]. Relative BMP over-expression results in an
12 epiphyseal cartilage phenotype and joint fusion, rather than in hyaline cartilage and normal joint
13 development. Synovial joint development is also critically dependent upon wingless (*wnt*) 4, *wnt9a*,
14 and *wnt 16* signalling within the interzone [24]. Whilst *wnt* signalling is not a requirement for joint
15 initiation, it is a requirement for proper development, including the formation of hyaline articular
16 cartilage. *Wnt4* and *wnt9a* knockout does not inhibit joint patterning but results in subsequent
17 fusion [24, 25]. The molecular regulation of early joint patterning is not limited to the interzone.
18 Indian hedgehog (IHH), expressed at the growth plate during long bone formation, also modulates
19 developing joint architecture and *Ihh* knockout is also characterised by joint fusion [26, 27].
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22 Interzone formation is followed by a process of joint cavitation that involves limited cell death [28],
23 alterations in fibrillar collagen from type I to type II [17], and differential growth of the joint
24 elements as the clefts join to form the central synovial cavity, lined by the developing synovium and
25 joint capsule [29]. The articular cartilage is formed by a layer of cells at the end of the epiphyseal
26 growth plate [30]. Peripherally, the interzone mesenchyme gives rise to the fibrous joint capsule and
27 supporting ligaments of the joint. Where the mesenchyme lines the capsule and articular surfaces,
28 the mesenchymal cells form the synovial membrane. These cells subsequently disappear from the
29 articular cartilage surface, probably as a result of joint movement.
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32 The process of joint cavitation is thought to occur largely through mechanically-induced changes in
33 the extracellular matrix [30, 31]. Although interzone formation occurs in the absence of movement,
34 skeletal muscle activity is required for both cavity formation and subsequent morphogenesis [14, 32-
35 34]. During this period there is also an increase in expression of CD44 and increased hyaluronan
36 synthesis that facilitates tissue separation and formation of a functional cavity [35], which is also
37 thought to be under mechanical regulation [36]. Studies show that muscle imbalance during
38 development results in abnormally-shaped joints [37-39]. There is also evidence that some signalling
39 mechanisms may be joint-specific [20, 40]. An overview of the signalling networks involved in
40 synovial joint development and their spatial colocalisation is shown in Figure 2 (adapted from [12]).
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43 Joint growth and modelling continues beyond embryogenesis and throughout post-natal growth to
44 skeletal maturity. This growth is regulated by a complex interplay of local molecular mechanisms
45 that are, in turn, also regulated at the long-range level.[41] These processes are reviewed in detail
46 elsewhere,[13, 42] but where perturbed, joint shape and surface congruity abnormalities may result
47 that can give rise to secondary osteoarthritis. In the following sections, we consider several common
48 complex conditions in which joint development is affected pre- or post-natally. The evidence base
49 for these conditions comes from the epidemiological literature that uses its own lexicon of terms.
50 For the purposes of this review, we use the term “risk factors” to mean variables that affect an
51 individual’s chance of developing a disease. We use the term “susceptibility” to mean the
52 individual’s overall chance of developing the disease. Note that the associations between individual
53 risk factors and overall disease susceptibility may be causal (in which there is a direct mechanistic
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link), or represent a marker for the disease for which the mechanism of the link is unclear but the two are clearly associated (such as through a third factor). The terms variant and single nucleotide polymorphism (SNP) are used synonymously. We use the term “common variant” to describe risk alleles with a frequency of >5% (or 0.05). Low-frequency variants have an allele frequency of between 1 and 5% (0.01 to 0.05), and rare variants have a frequency of <1% (or 0.01).

How does genetic variation influence joint architecture?

As outlined above, it is clear that a complex interplay of molecular signalling and mechanical events are required for normal synovial joint development. Whilst loss of function mutations within genes critical to synovial joint morphogenesis lead to generalised musculoskeletal skeletal abnormalities that may be incompatible with life, polymorphisms that arise in viable general populations also give rise to variations in joint shape that are heritable. The former group comprises a multitude of genetic mutations that provide critical insights into the functioning of individual genes required for normal musculoskeletal development. Here, we focus on common, complex disorders that arise within general populations and associate with the development of osteoarthritis. These disorders may be broadly classified into those that are captured within established disease definitions, and those that represent statistical shape variation within populations.

The hip is the most common site for established pathological variation in joint shape. Recognised disorders of hip joint morphology during growth include developmental dysplasia of the hip (DDH), Perthes’ disease, slipped capital femoral epiphysis (SCFE) and femoroacetabular impingement (FAI). These diseases describe discrete pathological entities that are associated with specific clinical shape phenotypes.

Developmental dysplasia of the hip

DDH, the most common skeletal dysplasia, is characterised by abnormal development of the hip joint and presents with varying severity from mild uncovering of the femoral head to complete dislocation of the hip joint and acetabular aplasia (Figure 3A) [43]. DDH has an incidence that ranges from 0.06 per 1,000 live births in individuals of African ancestry to 76.1 per 1,000 live births in Native Americans, and with an incidence in the UK European population of 3.6 per 1,000 [44]. The aetiology of DDH is complex, involving both environmental and genetic risk factors. Known associations include female sex, first-born, breech presentation, and family history[44].

Family studies have demonstrated that heritable factors contribute between 50% and 85% of the total DDH susceptibility [45-47]. Stevenson et al [48], in a familial aggregation study of 1649 distinct individuals from Utah, USA, with a DDH case: control ratio of 1:10, found a recurrent risk of 12 in first-degree relatives of those with DDH versus controls. Li et al [46], in a case-control familial study of Chinese individuals with DDH, reported a heritability of 84%, and a sibling recurrent risk of probands that was 10-fold that of the siblings of controls. Heritability may also be estimated at the population level amongst unrelated individuals using genome-wide association study (GWAS) analysis approaches. Hatzikotoulas et al [49], using genetic complex trait analysis [50] across 770 DDH cases and 3,364 controls in a discovery scan of 257,000 directly typed genetic variants with a minor allele frequency of >0.01, found that common variants explained 55% of the liability-scale heritability, and was equally distributed across chromosomes.

Genome-wide linkage analysis (GWLA) has identified several chromosomal regions segregating within large DDH pedigrees. Feldman et al [51], in a GWLA on an 18-member multigeneration family, the proband of which was severely affected by DDH, identified a 4 Mb region on chromosome 17q21. Candidate genes coded in this region are the *HOXB* cluster of homeobox genes,

1 *COL1A1* and *DLX3*. A Japanese GWLA of a 4-generation family containing eight patients with familial
2 osteoarthritis of the hip associated with acetabular dysplasia suggested linkage at 13q22 [52]. A
3 GWLA of a large South African family of European origin with Beukes hip dysplasia, an autosomal
4 dominant disorder of variable penetrance that is characterised by bilateral dysmorphism of the
5 proximal femur, mapped the causal gene to a 3.34 Mb region at 4q35 [53]. Several candidate gene
6 studies have also suggested associations between genetic variants and DDH, including *GDF5*, *TBX4*,
7 *ASPN*, and *IL6*, although only *GDF5* has been independently replicated and reached genome-wide
8 statistical significance levels (Table 1).
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11 Genome-wide association analysis enables a hypothesis-free approach to interrogating the entire
12 human genome for potential associations with a disease. In a GWAS of 770 DDH cases and 3364
13 population-based controls, Hatzikotoulas et al [49] identified eleven correlated variants at genome-
14 wide significance ($P < 5.0 \times 10^{-8}$) residing within the 5' untranslated region of *GDF5* (20q11.22).
15 Independent signals were replicated in three DDH cohorts of UK European ancestry, totalling 1,129
16 cases and 4,652 controls. Following meta-analysis, rs143384 in *GDF5* (OR [95% CI] 1.44 [1.34–1.56],
17 $P = 3.55 \times 10^{-22}$) was robustly associated with DDH, reaching genome-wide significance in both the
18 discovery and the replication cohorts. Gene-based association analysis in this cohort also implicated
19 variation within *UQCC1*, *MMP24*, and *RETSAT* at $P < 5 \times 10^{-8}$. *UQCC1* lies adjacent to *GDF5* and encodes
20 a trans-membrane protein ubiquinol-cytochrome-c reductase complex chaperone. *UQCC* is
21 expressed in differentiating chondrocytes and regulates growth control [54, 55]. Variants in this gene
22 are also associated with bone size [56], height [57] and hip axis length [58]. *MMP24* encodes a
23 member of the peptidase M10 family of matrix metalloproteinases that are involved in the
24 breakdown of extracellular matrix in embryonic development and tissue remodelling [59]. Sequence
25 variants within *MMP24* have also been associated with childhood height [60, 61]. *RETSAT* codes for
26 retinol saturase, an enzyme centrally involved in the metabolism of vitamin A [62]. Retinoic acid
27 signalling is essential for normal limb bud development, including bone and cartilage formation [63].
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33 ***Perthes' Disease***

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35 The term Perthes' disease describes idiopathic osteonecrosis of the femoral head in children.
36 Depending upon the age of onset and the capacity of the developing hip to remodel, the disease
37 results in femoral head and acetabular shape abnormalities of varying severity (Figure 3B). Perthes'
38 disease varies greatly in incidence between geographic areas and ethnic groups, but in Western
39 European populations the prevalence is typically between 5 and 15 per 100,000 children under the
40 age of 15 years [64]. The condition is thought to have a multifactorial inheritance pattern, with a
41 sibling and offspring recurrent risk of 2.6% in the UK, based upon the family history of 412 index
42 cases [65]. In a recent study using the Danish Twin Register, Metcalfe et al examined 81 twin pairs
43 [66] and identified a familial clustering but no genetic component, with an overall proband
44 concordance of 0.09. Although several small case control association studies of the disease have
45 been conducted, including a meta-analysis of hypercoagulability genetic polymorphisms totalling
46 824 cases and 2,033 controls [67], only variation within Factor V Leiden thrombophilia (an inherited
47 disorder of blood clotting) was identified as a possible risk locus (pooled OR 3.10 [95%CI 1.68-5.72])
48 [67]. Thus, although geographic and familial clustering is clear in Perthes' disease, the genetic
49 component appears to be small. However, this may be due to the limited sample size and hence
50 power of studies to date.
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56 ***Slipped Capital Femoral Epiphysis***

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58 Slipped capital femoral epiphysis (SCFE) is a disorder of the hip that is characterised by displacement
59 of the capital femoral epiphysis from the metaphysis through the physis, and results in a
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1 characteristic shape abnormality of the hip joint (Figure 3C). It is a disorder of the adolescent
2 developing hip, is more common in males, and has an incidence that is similar to that of Perthes'
3 disease [68]. The condition is thought to have an endocrine aetiology and can cluster in families [69,
4 70], but to date, powered studies to determine any heritable component have not been conducted..

5 ***Femoroacetabular impingement***

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7 The term FAI describes morphological abnormalities of the femoral head–neck junction, acetabulum,
8 or both, resulting in abnormal contact between the proximal femur and the pelvic acetabulum at the
9 hip joint [71]. Two basic pathologies are described. In “Cam” morphology, a non-spherical extension
10 of the femoral head-neck junction (usually anterolateral) causes abutment into the adjacent
11 acetabular cavity [72] (Figure 3D). In “Pincer” morphology, local or global over-coverage of the
12 acetabulum results in linear impact of the acetabular rim against the head-neck junction [73] (Figure
13 3E). The two deformities may also coexist in “Combined” lesions. The FAI hip shape abnormality
14 develops during the adolescent phase of skeletal growth before closure of the growth plate and has
15 been associated with higher levels of sporting activity [74], although a causal link to exercise remains
16 unclear. Asymptomatic FAI is highly prevalent (estimated at up to 75%) in populations of European
17 descent (with cam lesions being more common in males) but is rare in Asian populations [75-78].

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19 The heritable basis of FAI as a distinct hip shape abnormality has not yet been studied in depth. This
20 is perhaps unsurprising, as its development can only be definitively determined at closure of growth
21 plate [79], and there are few clinical reasons to image the hip in asymptomatic young adults.
22 However, small-scale analyses do exist. Pollard et al compared 96 siblings (mean age 38 years) of 64
23 patients (mean age 36) treated for FAI with a spouse control group of 77 individuals (mean age 42)
24 and found a relative risk of cam morphology of 2.8 (95%CI 1.8 to 4.2) and of pincer morphology of
25 2.0 (1.3 to 3.0). Pollard et al also examined familial associations in ‘sibkids’ [80], a cohort with a
26 hereditary predisposition to hip osteoarthritis, and estimated an odds ratio for cam morphology of
27 2.1 (1.3 to 3.5) versus spouse controls but no differences in pincer morphology or dysplasia.
28 However, subjects were examined in mid-life when degenerative change is prevalent and a possible
29 common environment underpinning of the associations were not examined. To date, no well-
30 powered genome-wide or candidate variant analyses have been published that examine the
31 relationship between specific genetic risk factors and conventional radiographic indices of FAI.

32 ***Population level variation in joint shape***

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34 At the population level, computer vision methods have been applied to examine joint shape
35 variation, although these phenotypes do not directly map to the clinical diagnoses of FAI or DDH.
36 Statistical shape analysis describes the shape of a deformable object by applying principal
37 component analysis to a set of landmark points, and assumes each shape is a deformed version of a
38 reference shape. Statistical shape models (SSM) may be applied to both 2-dimensional (2-D) and 3-D
39 medical images [81]. SSMs have been used to describe the principal sources of population variation
40 in shape at both the hip and the knee [82-85], and to describe those associated with trochlear
41 dysplasia [86] and acute anterior cruciate ligament injury [87]. In the setting of FAI, SSMs have also
42 been used to compare cam lesion deviation from the population reference femoral head-neck shape
43 in pre-operative planning for surgical intervention [88].

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45 The epidemiology of bone geometry has been of interest in the exploration of the association
46 between hip shape and osteoporotic fracture risk. In meta-analyses of overlapping patient cohorts,
47 Baird et al[89], and Hsu et al[90] examined genome-wide genotyped datasets in patients with DXA
48 scans of the hip to identify relationships with proximal femoral SSMs and conventional measures of
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1 hip geometry, respectively. Baird et al used SSMs to examine shape-genotype associations in
2 ~16,000 individuals across ~7 million SNPs, identifying 8 independent genome-wide significant
3 variants (Bonferroni-corrected $P < 5 \times 10^{-9}$) that were associated with 3 modes of joint shape variation
4 [89]. Seven of the variants were located within 200kb of genes involved in endochondral ossification
5 (*SOX9*, *PTHrP*, *RUNX1*, *NKX3-2*, *FGFR4*, *DICER1*, and *HHIP*), suggesting possible association with bone
6 formation and by extension, joint shape. Hsu et al examined conventional DXA-derived hip structural
7 analysis in 18,719 men and women. Using linkage disequilibrium (LD) score regression [91], they
8 found that nominally-associating variants explained 12%, 13%, 18%, and 22% of the heritable
9 variation in neck-shaft angle, femoral neck length, neck section modulus, and narrowest neck width,
10 respectively. Following replication in independent cohorts, independent variants near
11 *IRIX/ADAMTS16*, *LRP5/PPP6R32/GAL*, *CCDC91*, *FGFR4*, *NSD1*, and *RAB24* met genome-wide
12 significance.
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16 In a GWAS of bone area as a proxy for bone size quantitated by DXA, Stykarsdottir et al identified 12
17 loci that are associated with hip or vertebral size [92], examining 33.4 million sequence variants in
18 Icelandic subjects across 28,954 hip scans and 29,059 lumbar spine scans. They identified rs143384
19 (20q11.22) in the *GDF5* 5'UTR as a locus for total hip ($\beta = 0.071$, $P = 2.2 \times 10^{-22}$) and trochanteric area
20 ($\beta = 0.071$, $P = 1.1 \times 10^{-18}$). This locus had previously been robustly associated with DDH in the GWAS by
21 Hatzikotoulas et al [49]. They also identified 2 other hip area loci, 17q24.3 in an intergenic region
22 near *SOX9* (intertrochanteric area $\beta = 0.072$, $P = 6.2 \times 10^{-18}$) and 4q31.21 in the 5'UTR of *HHIP* (femoral
23 neck area $\beta = 0.054$, $P = 8.4 \times 10^{-14}$), that had previously been associated with hip shape SSMs in the
24 Baird GWAS meta-analysis [89].
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30 **Joint shape is an important risk factor for OA**

31 ***Conventional measures of joint shape and OA susceptibility***

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33 It has long been recognised that pathological developmental abnormalities of the hip joint such as
34 DDH, Perthes' disease, and SCFE commonly result in osteoarthritis and hip replacement [49, 93-95].
35 For example, individuals with mild DDH are 10 times more likely to develop OA compared with DDH-
36 free controls [96]. It has only been more recently appreciated that subtle variations in joint shape
37 also predispose to degenerative change. Such variations in joint shape are commonly measured on
38 plain radiographs in clinical practice to describe joint geometry (see Figure 4 for common indices and
39 their definitions). Observations by Murray [97], and later by Solomon [98] and Harris [99], estimate
40 that over 90% of individuals with idiopathic hip OA exhibit subtle variations in acetabular and
41 proximal femoral shape that precede the degenerative process (Figure 5). These deformities are
42 highly prevalent in European populations and can result in a focal mechanical overload of articular
43 cartilage, leading to subsequent OA [72, 73, 100]. Doherty et al [101], in a study of plain
44 anteroposterior radiographs of the hip in 965 OA cases and 1,111 controls without radiographic OA,
45 found the presence of cam morphology in at least 1 hip in 18% of cases versus 4% of controls (OR
46 6.95; 95%CI 4.64 to 10.41). An abnormal femoral head-to-neck ratio was present in 24% in cases
47 versus 4% in controls (OR 12.01; 8.05 to 18.15). As the femoral head-to-neck ratio decreased, the
48 presence of hip OA also rose.
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55 Demonstration that the converse is also true was made by Kim in 1989, reporting a high incidence of
56 hip joint congruity and low incidence of both DDH and of OA in the Korean population [102]. Dudda
57 et al [103], compared morphological features associated with FAI in females from a Chinese cohort
58 (Beijing OA Study) versus white women from the United States participating in the Study of
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1 Osteoporotic Fractures. They found low lateral centre-edge angles suggesting dysplasia ($<20^\circ$) more
2 often in the Chinese (22% of hips versus 7% in whites, $p=0.005$), whilst low mean impingement
3 angles (83.6° versus 87.0° , $p=0.03$) and lateral centre-edge angles suggestive of impingement (23%
4 versus 11%, $p=0.008$) were more common in women of European descent. More recently, Edwards
5 et al examined hip plain radiographic morphological characteristics in individuals of European
6 descent, African Americans and Chinese men and women with no radiographic hip OA [104]. They
7 found that the Chinese group had more shallow and narrow acetabular sockets, reduced femoral
8 head coverage, smaller femoral head diameter, and a lesser femoral neck-shaft angle versus the
9 other ethnic groups. Taken together, these findings are consistent with the epidemiological
10 observation that idiopathic OA is more prevalent in Europeans [105], whilst in Asian populations hip
11 OA is more commonly associated with a DDH morphology.
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14 Deformities associated with cam-type FAI and subtle DDH morphology are also independent
15 predictors of incident radiographic OA and progression to hip replacement in longitudinal studies.
16 Nicholls et al [106], found that cam morphology, identified by an alpha angle of greater than 65° ,
17 had an increased risk of radiographic OA and hip replacement over 2 decades [107], with each
18 degree increase in alpha angle conferring a 5% and 3% increase in risk respectively. Agricola et al
19 found similar relationships between increasing alpha angle ($>$ cam morphology) and OA progression
20 in the CHECK cohort [108]. Thomas et al [107], found that mild DDH increased the risk of
21 radiographic OA development and hip replacement over 2 decades, with each degree reduction in
22 lateral centre edge angle below 28° associated with a 14% and 21% increase in risk of OA and hip
23 replacement, respectively [107]. However, no clear associations have been identified between
24 isolated pincer-type FAI and future OA risk [106-109].
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29 ***Statistical models of joint shape and OA susceptibility***

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31 SSMs capture information that is predictive of OA and that is not present in pre-defined radiographic
32 geometric measures, and vice versa. When combined, they add to the predictive value for incident
33 OA above clinical risk factors. Waarsing et al [110], examined DXA images of the hip in 218 men and
34 women with established hip OA followed over 2 years. They demonstrated that various shape and
35 texture modes correlated with clinical pain and function scores where plain radiographic measures
36 (Kellgren-Lawrence (KL) score and minimum joint space width) did not. Castaño-Betancourt et al
37 [111], used SSMs and predefined geometry parameters derived from baseline plain hip radiographs
38 to predict incident radiographic OA (KL score ≥ 2) over 6.5 years in 688 individuals from the
39 Rotterdam Study. They found that hip geometry alone was of similar predictive value to clinical risk
40 factors of sex, age, and body mass index; and when combined, added 7% to the prediction obtained
41 by clinical risk factors alone (AUC = 0.67 (geometry), 0.66 (clinical), 0.73 (geometry + clinical))[111].
42 Agricola et al demonstrated in female participants in the CHECK and Chingford cohorts that baseline
43 (KL <2) radiograph-derived hip SSMs were also associated with future THR [112].
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49 SSMs are also emerging as a useful phenotyping tool to improve our understanding of the
50 relationship between genotype and joint shape. In the first of such studies, Baker-LePain et al [113],
51 examined the association of candidate variants within the wnt antagonist *FRZB* with radiograph-
52 derived hip shape SSMs in a nested subsample (European-ancestry women ≥ 65 years; 451 hip OA
53 cases, 601 controls) from the Study of Osteoporotic Fractures. They found no association between
54 genotype and case-control status or with acetabular depth or centre edge angle, but a weak
55 association with mode 2 (amongst 10 modes) in subjects having at least 1 copy of the rs288326 or
56 the rs7775 *FRZB* minor allele ($P=0.019$ for each test). A subsequent analysis stratified by presence of
57 the rs288326 minor allele showed a weak positive association between the upper quartile of
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1 subjects for mode 2 with OA in those carrying the variant allele ($P=0.02$), which led them to propose
2 that genetic variation within *FRZB* may modulate the effect of hip shape on OA risk.

3 Subsequently, Lindner et al examined 41 candidate genetic variants (that had previously been
4 associated with OA or hip morphology) and plain anteroposterior radiographs of the non-OA
5 affected hip in 929 patients from the arcOGEN cohort [114, 115]. In univariate analysis they
6 identified an association between rs4836732 (within *ASTN2*) and mode 5 of the female SSM
7 ($p=0.0016$), and between rs6976 (within *GLT8D1*) and mode 7 of the mixed sex SSM ($p=0.0003$). The
8 multivariate analysis identified association between rs5009270 (near *IFRD1*) and a combination of
9 modes 3, 4, and 9 of the mixed-sex SSM ($p=0.0004$). In the Baird et al hip shape GWAS [89], 3 of the
10 genome-wide significant variants that were associated with shape mode variation are also
11 established loci for hip OA, rs4836732 (intronic variant within *ASTN2*), rs10743612 (intergenic
12 variant downstream of *PTHLH*), and rs73197346 (intergenic variant upstream of *RUNX1*).
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16 Fewer studies have examined the relationship between SSMs and knee OA. Haverkamp et al
17 examined differences in knee shape by SSMs between women with prevalent knee OA versus those
18 without OA in Rotterdam Study participants.[116] They found that the women with knee OA had
19 SSMs that described a broader femur and tibia and also an elevated lateral tibial plateau, findings
20 that are consistent with plain radiographic features in the presence of knee OA. Wise et al [117], in a
21 study of 304 knees with ($KL\geq 2$) versus 304 knees without ($KL<2$) incident OA from the Osteoarthritis
22 Initiative found that SSMs of distal femoral and proximal tibial shape derived from plain
23 anteroposterior knee radiographs only weakly and inconsistently modulated the relationship
24 between sex and incident knee OA.
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28 ***Bone shape remodelling in response to OA***

29 Care is required when interpreting the results of joint shape and OA susceptibility association
30 analyses, as joint shape changes with OA severity. Gregory et al [118] used SSMs of the proximal
31 femur derived from plain radiographs of the hip at baseline and again after 6 years in 110
32 participants in the Rotterdam Study to quantify the deforming effect of OA progression on the
33 proximal femur, and first proposed SSMs as an imaging biomarker of hip OA progression. Similarly,
34 Hunter et al [119], conducted a nested case-control study of knee MRI data within the Osteoarthritis
35 Initiative and showed that bone area increased and shape changed more over 24 months in OA
36 cases versus controls (OR case/control 1.28 to 1.71 for area, and 1.22 to 1.64 for shape per SD
37 change in each variable, respectively).
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43 Such observations make the disentangling of causation from association challenging, particularly
44 where low-resolution modalities such as DXA are used in isolation to define the joint shape and
45 absence of OA at baseline. Further, DXA images present a distorted image of the hip that is
46 magnified in the x-axis, because of the fan-beam image acquisition [120]. These limitations are not
47 confined to DXA data, but may impact all SSMs based on 2-D imaging. For example, as OA progresses
48 at the hip, fixed external rotation of the hip occurs that may also give the impression of a change in
49 bone area or femoral neck-shaft angle. Similarly, femoral head osteophytes lead to high alpha angles
50 seen in Cam morphology, and lateral acetabular osteophytes produce pincer morphology. Cross-
51 sectional imaging modalities do not suffer such artefacts to the same extent. Recently, Inamdhar et al
52 [121] conducted a 36-month longitudinal MRI study of variation in proximal femur 3D morphological
53 shape (3D-SSM) and associations with cartilage health in 46 men and women with developing hip
54 osteoarthritis. They showed that 3D-SSM characterising increases in head and neck volume and
55 decreasing femoral neck anteversion were weakly associated with progression of symptoms and
56 MRI-identified cartilage lesions.
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1 Bone remodelling features have also been used to define different phenotypes within established
2 OA into normotrophic, hypertrophic, or atrophic, depending upon the resultant bone shape [122].
3 These differences in bone remodelling responses may also have genetic correlates that further
4 impact on the observed genetic relationships between joint shape and OA. Panoutsopoulou et al
5 [123], examined the effect of clinically relevant endophenotyping according to site of maximal joint
6 space narrowing (maxJSN) and bone remodelling response in a stratified GWAS of the arcOGEN
7 dataset, comparing 2,118 radiographically-defined hip OA cases and 6,500 population based
8 controls. They found that variation within *LRCH1* was associated with site of maximal joint space
9 narrowing (OR 0.70; 0.61 to 0.80), whilst variation adjacent to *STT3B* was associated with a
10 hypertrophic pattern of remodelling (OR 1.45; 1.24 to 1.69). Both associations were completely
11 attenuated in the non-stratified analyses. Further, *STT3B* was over-expressed in OA-affected versus
12 intact human cartilage in an analysis of hypertrophic versus atrophic bone remodelling pattern.
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18 **Evidence from OA susceptibility studies**

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20 Our understanding of the genetic epidemiology of OA has increased substantially over the last few
21 years with the number of genome-wide scans reported on increasingly large patient cohorts. To
22 date, these efforts have resulted in almost 100 robustly replicating genome-wide significant OA risk
23 loci being identified [124-129]. The vast majority of these risk loci represent common variants with a
24 small to moderate effect size, consistent with the complex and highly polygenic architecture of the
25 disease (Figure 6). However, large-scale GWAS datasets are not commonly accompanied by
26 radiographic phenotype data upon which to examine relationships with joint shape.
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30 Zengini et al [124], in a GWAS of the UKBiobank meta-analysed with other cohorts totalling 30,727
31 cases and 297,191 controls examining 16.5 million variants identified 9 novel, robust OA variants.
32 They also conducted a nested substudy of osteoarthritis-related plain radiographic phenotypes in
33 mixed cohorts of smaller size (where radiographic data were available). Of the 9 identified variants
34 in the primary analysis, several were associated with the minimum joint space width phenotype, but
35 only a nominal association between an intergenic variant rs116882138 and centre-edge angle (a
36 feature of DDH, $\beta=-1.1388$, $P=0.03$), and no association with alpha angle (a feature of cam
37 morphology), was found. Tachmazidou et al [125], in the largest GWAS of OA published to date,
38 including 77,052 cases and 378,169 controls in a meta-analysis examining 17.5million variants,
39 identified 64 signals (52 novel) at $MAF>0.01$ on top of 34 previously established loci [124, 126, 128,
40 130-142]. Pathways analysis using MAGMA, PASCAL, and DEPICT identified 64 biological processes,
41 46 of which are involved in bone, cartilage, or chondrocyte morphogenesis. Although associations
42 with other demographic characteristics and disease states were examined by linkage disequilibrium
43 regression analysis using LDHub [91], specific direct associations with joint shape were not explored.
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50 **What consistent signals arise from both joint shape and OA studies?**

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52 Although many studies have examined the genetics of OA, relatively few have examined the genetics
53 of diseases of joint shape or the relationships between shape, joint shape disorders and OA.
54 Hatzikotoulas et al , used LD regression to estimate the genetic correlation between DDH and hip OA
55 in the UK Biobank hip OA dataset, identifying a positive genetic correlation ($rg=0.58$ (s.e.=0.21),
56 $P=0.0047$), but did not distinguish between a causal relationship versus shared genetic causes. Baird
57 et al [143], examined the relationship between 11 genetic loci for hip OA and DXA-derived hip shape
58 in 3,111 women participating in the Avon Longitudinal Study of Parents and Children. They identified
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1 associations with at least nominal significance between 3 OA risk loci (*KLHDC5/PTHLH* rs10492367,
2 *DOT1L* rs12982744, and *COL11A1* rs4907986) and hip shape. Co-localisation analysis indicated
3 sharing of genetic signals for hip shape and hip OA for the *KLHDC5/PTHLH* and *COL11A1* loci.
4 However, the cohort was not screened for the presence of radiographic OA prior to inclusion in the
5 analysis and thus hip shape variation resulting from OA, rather than predisposing to it, cannot be
6 excluded.
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8 Whilst many risk loci that lie adjacent or within genes that have a role in mesenchymal cell function
9 have been associated with subtle statistical variations in joint shape or OA susceptibility, relatively
10 few specific genes have been consistently identified across both the joint shape and the
11 osteoarthritis phenotypes. Some of the key implicated genes are outlined below.
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13 Growth Differentiating Factor 5 (*GDF5*), a member of the TGF β signalling family, is a key regulator of
14 joint morphogenesis. Mutations in *GDF5* results in brachydactyly and symphalangism [144].
15 Variation within *GDF5* has also been widely associated with DDH [49], and also with hip
16 osteoarthritis across multiple populations [124, 130]. Pooled evidence for association from two
17 independent Japanese studies attained genome-wide significance with allelic OR [95%CIs] of 1.79
18 [1.53 -2.09], $p=2\times 10^{-13}$ [130]. This *GDF5* SNP was later associated with knee OA in individuals of
19 European descent in a subsequent meta-analysis across a total of 6,861 knee OA cases and 10,103
20 controls, with allelic OR [95%CIs] of 1.16 [1.10-1.22], $p=9.6\times 10^{-9}$ [145], and in hip and knee OA
21 across 30,727 cases and 297,191 controls [124]. Chen et al [146] have shown that the *GDF5* locus
22 contains many separate regulatory elements that control expression of the gene at different joint
23 sites, and that these flanking regions are large. Capellini et al of the same group have also recently
24 described a novel enhancer region GROW1 in an extended downstream regulatory region of *GDF5*
25 [147]. Most recently, the same group has used chondrocyte chromatin datasets to propose a model
26 linking evolutionary genetic variations within the *GDF5-UQCC1* risk locus (rs6060369) that perturb
27 regulatory constraint during knee development with subsequent knee OA in adult mice, and suggest
28 an ortholog in chondrocyte evolution of the modern human knee that affects bone shape.[148]
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35 SOX9 is a pivotal transcription factor during joint development and in adulthood, committing
36 mesenchymal progenitors to the chondrocyte lineage, activating cartilage-specific genes and
37 modulating chondrocyte survival. SOX9 deficiency, generally due to spontaneous mutations at the
38 17q24 locus, causes campomelic dysplasia that is characterised by multiple long bone abnormalities,
39 including brachydactyly and dislocation of the hips [149]. Common variation within *SOX9* is
40 associated with both OA and joint shape variation [89, 92, 125]. *SOX9* lies within a relatively gene-
41 free region on chromosome 17, with large domains (1.9Mb upstream and 0.5Mb downstream) that
42 facilitate interaction with cis-acting elements causing SOX9-dependent diseases [150].
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46 Parathyroid hormone-like hormone, encoded by *PTHLH*, regulates endochondral bone formation as
47 a downstream signalling pathway to RUNX2, through its receptor's inhibitory action on chondrocyte
48 development and differentiation and pro-osteoblastic activity [151]. Mutations in *PTHLH* cause
49 brachydactyly and short stature [152], whilst common variation at the *PTHLH* locus is associated
50 with hip shape and OA [128, 143].
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53 Collagen type XI, encoded by *COL11A1*, is an important component of the growing skeleton, but its
54 presence in the adult is mainly confined to articular cartilage and the intervertebral disc. Loss of
55 function mutations in *COL11A1* cause fibrochondrogenesis type 1, a disorder characterised by severe
56 skeletal abnormality and is usually fatal in early life; and Stickler and Marshall syndromes, disorders
57 characterised by less severe bone and joint abnormalities that are non-fatal. Common variation in
58 *COL11A1* is associated with hip shape variation and has been suggestively associated with hip OA,
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1 although not at genome-wide significance [114, 143]. The molecular mechanisms of these proposed
2 variants on *COL11A1* expression remain to be clarified.

3 Astrotactin 2, encoded by *ASTN2*, is most strongly expressed in the brain and plays a role in neuronal
4 migration. *ASTN2* deletion causes autism and schizophrenia. Despite the apparent lack of relation to
5 joint morphogenesis and OA, common variation in *ASTN2* is robustly associated with both hip shape
6 and OA [89, 115, 128]. Although a proposed mechanism relating to pain sensing and OA
7 symptomatology has been suggested, this does not readily explain the shape association.
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10 Although variation in genes identified in the studies outlined above, including *COL11A1*, *DOT1L*, *IHH*,
11 *RUNX1*, *RETSAT*, and many others may also link joint development with subsequent OA, they have
12 not been specifically included here, as they are yet to be established with both phenotypes at
13 genome-wide significance
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18 **Conclusions**

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20 The study of increasingly large genome-wide meta-analyses together with multi-omics at scale, is
21 starting to revolutionise our understanding of the heritable biology of osteoarthritis. We have
22 established that 60% and 40% of susceptibility to hip and knee OA, respectively, is heritable. Current
23 international initiatives, such as the GO Consortium [https://www.genetics-
25 osteoarthritis.com/home/index.html](https://www.genetics-
24 osteoarthritis.com/home/index.html) will further expand the depth and breadth of our
26 understanding of the contribution of common and low-frequency variants to disease heritability.
27 Study of the heritable biology of joint shape, and how it relates to OA risk, thus far, is yet to benefit
28 from the same advantages of scale and phenotype specificity. Advances have been made in
29 understanding the contribution of hip shape to OA risk, and shape variation can be measured with
30 varying degrees of accuracy by several methods. However, for OA at other sites including the knee,
31 clear shape phenotypes are less readily identified. The influence of other risk factors, such as sex,
32 obesity and joint injury at the knee also make establishing relationships between joint shape and
33 genotype more complex. Future abilities to link relevant imaging data to clinical and genomic
34 datasets will narrow this gap.
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Study Reference	Gene/loci	Chromosomal location	Study design	SNP variant	Phenotype	Study Population(s)
Feldman et al. 2010 [51]	17q21.31-17q22	17q21.31-17q22	GWLA	-	DDH	American and Chinese
Mabuchi et al. 2006 [52]	13q22	13q22	GWLA	-	DDH	Japanese
Watson et al. 2015 [53]	<i>UFSP</i>	4q35	GWLA and exome sequencing	c.868T > C	Beukes hip dysplasia	South African
Feldman et al. 2013 [153]	<i>CX3CR1</i>	3p22.2	GWLA and exome sequencing	rs3732378	DDH	American
Basit et al. 2017 [154]	<i>HSPG2</i>	p. Ala1110Ser	GWLA and exome sequencing	c.3328G > T	DDH	Saudi Arabian
Basit et al. 2017 [154]	<i>ATP2B4</i>	p. Arg755Gln	GWLA and exome sequencing	c.2264G > A	DDH	Saudi Arabian
Dai et al. 2008 [155], and Hatzikotoulas et al. 2018 [49]	<i>GDF5</i>	20q11.22	CGAS GWAS and subsequent replication	rs143383, rs143384	CDH DDH	Chinese females United Kingdom
Wang et al. 2010 [156]	<i>TBX4</i>	17q23.2	CGAS	rs374448	DDH	Chinese
Shi et al. 2011 [157]	<i>ASPN</i>	9q22.31	CGAS	D-repeat polymorphism of ASPN	DDH	Chinese
Cengic et al. 2015 [158]	<i>IL6</i>	7p15.3	CGAS	rs1800796	DDH	Croatian
Cengic et al. 2015 [158]	<i>TGFB1</i>	19q13.2	CGAS	rs1800470	DDH	Croatian
Jia et al. 2012 [159]	<i>PAPPA2</i>	20q11.22	CGAS	rs726252	DDH	Chinese
Hao et al. 2014 [160]	<i>HOXB9</i>	17q21.32	CGAS	rs2303486	DDH	Chinese
Tian et al. 2012 [161]	<i>HOXD9</i>	2q31.1	CGAS	rs711819	DDH	Chinese females
Liu et al. 2014 [162]	<i>DKK1</i>	10q21.1	CGAS	rs1569198	DDH	Chinese
Zhao et al. 2013 [163]	<i>COL1A1</i>	17q21.33	CGAS	rs113647555	DDH	Chinese females
Sun et al. 2015 [164]	<i>UQCC</i>	20q11.22	GWAS	rs6060373	DDH	Chinese

Table 1. Summary of the published genetic associations with DDH. GWLA: genome-wide linkage analysis. CGAS: candidate gene association study. GWAS: genome-wide association study.

Legend to figures

Figure 1. Synovial joint development in the mouse. Longitudinal views depicting key steps in the formation of the knee joint. a) The first sign of a presumptive joint is a condensation of Col2+ limb bud progenitors at the presumptive joint site; b) Joint specification is marked by induction of Gdf5 in the interzone and downregulation of Col2a1; c) A joint space is formed by cavitation after progenitors for a variety of secondary joint structures are specified from the Gdf5+ progenitor pool; d) Maturation of the synovial joint of the knee occurs during development and early postnatal life. Reproduced from Salazar et al [165], with permission.

Figure 2. Spatial expression patterns (A) and principal signaling pathways (B) in synovial joint development. The expression domains of critical signaling pathway components are regionally restricted during development of synovial joints. AC, articular cartilage; IZ, interzone; JC, joint capsule. Reproduced from Salva et al [12], with permission.

Figure 3. Disorders of the growing hip joint. A) Bilateral hip dysplasia in a skeletally-mature individual. The acetabuli are typically shallow and steep, and there is extrusion of the femoral heads with evidence of decreased lateral coverage (arrows); B) Perthes' disease of the right hip in a skeletally mature individual. The right femoral head is broad and flattened and the corresponding acetabulum is similarly shaped (arrow). C) Slipped capital femoral epiphysis of the left hip in an adolescent male. The epiphysis has slipped posteromedially from the physis (arrow); D) Bilateral cam lesions in a skeletally maturing male, arrows show lateral head-neck junction prominence; E) Bilateral pincer lesions in a skeletally mature male, arrows show over-coverage of femoral head.

Figure 4: Acetabular and proximal femoral morphological parameters associated with OA risk. a) HTE= horizontal toit externe , SA=Sharp's angle, and AT=acetabular tilt; b) AIDWR=acetabular index of depth to width ratio; c) LCEA=lateral centre-edge angle and AA=alpha angle; d) FHFNR=femoral head to femoral neck ratio and FNLWR=femoral neck length to width ratio; e) MPFA=modified proximal femoral angle and FNSA=femoral neck-shaft angle.

Figure 5. The biomechanical consequences of non-normal hip shape. Illustration shows relationship between out of range hip shape parameters and the development of osteoarthritis.

Figure 6. Effect size and risk allele frequency of published osteoarthritis genetic risk loci. Each circle represents a published osteoarthritis risk single-nucleotide variant plotted with its odds ratio (OR; y axis) as a function of the risk allele frequency (x axis). The different size and colour of each circle shows the sibling relative risk ratio (λ_s) and the percentage of variance explained on the liability scale respectively (h^2_L ; calculated assuming 13.5% prevalence of OA). Gene annotations are taken from the Ensembl genome browser (human assembly GRCh37). The majority are common variants with small ($OR < 2.0$) effect sizes, only those with $OR > 2.0$ are named here.

References

1. Disease GBD, Injury I, Prevalence C (2016) Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 388:1545-1602
2. Global Burden of Disease Study C (2015) Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 386:743-800
3. Nuesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Juni P (2011) All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. *BMJ* 342:d1165
4. Yelin E, Murphy L, Cisternas MG, Foreman AJ, Pasta DJ, Helmick CG (2007) Medical care expenditures and earnings losses among persons with arthritis and other rheumatic conditions in 2003, and comparisons with 1997. *Arthritis Rheum* 56:1397-1407
5. Murphy LB, Cisternas MG, Pasta DJ, Helmick CG, Yelin EH (2018) Medical Expenditures and Earnings Losses Among US Adults With Arthritis in 2013. *Arthritis Care Res (Hoboken)* 70:869-876
6. MacGregor AJ, Antoniadou L, Matson M, Andrew T, Spector TD (2000) The genetic contribution to radiographic hip osteoarthritis in women: results of a classic twin study. *Arthritis Rheum* 43:2410-2416
7. Manek NJ, Hart D, Spector TD, MacGregor AJ (2003) The association of body mass index and osteoarthritis of the knee joint: an examination of genetic and environmental influences. *Arthritis Rheum* 48:1024-1029
8. Magnusson K, Turkiewicz A, Englund M (2019) Nature vs nurture in knee osteoarthritis - the importance of age, sex and body mass index. *Osteoarthritis Cartilage* 27:586-592
9. Griffin DR, Dickenson EJ, Wall PDH, Achana F, Donovan JL, Griffin J, Hobson R, Hutchinson CE, Jepson M, Parsons NR, Petrou S, Realpe A, Smith J, Foster NE, Group FAS (2018) Hip arthroscopy versus best conservative care for the treatment of femoroacetabular impingement syndrome (UK FASHIoN): a multicentre randomised controlled trial. *Lancet* 391:2225-2235
10. Palmer AJR, Ayyar Gupta V, Fernquest S, Rombach I, Dutton SJ, Mansour R, Wood S, Khanduja V, Pollard TCB, McCaskie AW, Barker KL, Andrade T, Carr AJ, Beard DJ, Glyn-Jones S, Group FS (2019) Arthroscopic hip surgery compared with physiotherapy and activity modification for the treatment of symptomatic femoroacetabular impingement: multicentre randomised controlled trial. *BMJ* 364:l185
11. Dwyer T, Whelan D, Shah PS, Ajrawat P, Hoit G, Chahal J (2020) Operative Versus Nonoperative Treatment of Femoroacetabular Impingement Syndrome: A Meta-analysis of Short-Term Outcomes. *Arthroscopy* 36:263-273
12. Salva JE, Merrill AE (2017) Signaling networks in joint development. *Dev Dyn* 246:262-274
13. Chijimatsu R, Saito T (2019) Mechanisms of synovial joint and articular cartilage development. *Cell Mol Life Sci* 76:3939-3952
14. Mitrovic DR (1977) Development of the metatarsophalangeal joint of the chick embryo: morphological, ultrastructural and histochemical studies. *Am J Anat* 150:333-347
15. Jenner F, A II, Cleary M, Heijnsman D, Narcisi R, van der Spek PJ, Kremer A, van Weeren R, Brama P, van Osch GJ (2014) Differential gene expression of the intermediate and outer interzone layers of developing articular cartilage in murine embryos. *Stem Cells Dev* 23:1883-1898
16. Holder N (1977) An experimental investigation into the early development of the chick elbow joint. *J Embryol Exp Morphol* 39:115-127

17. Craig FM, Bentley G, Archer CW (1987) The spatial and temporal pattern of collagens I and II and keratan sulphate in the developing chick metatarsophalangeal joint. *Development* 99:383-391
18. Hotten G, Neidhardt H, Jacobowsky B, Pohl J (1994) Cloning and expression of recombinant human growth/differentiation factor 5. *Biochem Biophys Res Commun* 204:646-652
19. Storm EE, Huynh TV, Copeland NG, Jenkins NA, Kingsley DM, Lee SJ (1994) Limb alterations in brachypodism mice due to mutations in a new member of the TGF beta-superfamily. *Nature* 368:639-643
20. Storm EE, Kingsley DM (1996) Joint patterning defects caused by single and double mutations in members of the bone morphogenetic protein (BMP) family. *Development* 122:3969-3979
21. Francis-West PH, Abdelfattah A, Chen P, Allen C, Parish J, Ladher R, Allen S, MacPherson S, Luyten FP, Archer CW (1999) Mechanisms of GDF-5 action during skeletal development. *Development* 126:1305-1315
22. Brunet LJ, McMahon JA, McMahon AP, Harland RM (1998) Noggin, cartilage morphogenesis, and joint formation in the mammalian skeleton. *Science* 280:1455-1457
23. Francis-West PH, Parish J, Lee K, Archer CW (1999) BMP/GDF-signalling interactions during synovial joint development. *Cell Tissue Res* 296:111-119
24. Spater D, Hill TP, Gruber M, Hartmann C (2006) Role of canonical Wnt-signalling in joint formation. *Eur Cell Mater* 12:71-80
25. Spater D, Hill TP, O'Sullivan R J, Gruber M, Conner DA, Hartmann C (2006) Wnt9a signaling is required for joint integrity and regulation of Ihh during chondrogenesis. *Development* 133:3039-3049
26. Vortkamp A, Lee K, Lanske B, Segre GV, Kronenberg HM, Tabin CJ (1996) Regulation of rate of cartilage differentiation by Indian hedgehog and PTH-related protein. *Science* 273:613-622
27. Lanske B, Karaplis AC, Lee K, Luz A, Vortkamp A, Pirro A, Karperien M, Defize LH, Ho C, Mulligan RC, Abou-Samra AB, Juppner H, Segre GV, Kronenberg HM (1996) PTH/PTHrP receptor in early development and Indian hedgehog-regulated bone growth. *Science* 273:663-666
28. Ballard KJ, Holt SJ (1968) Cytological and cytochemical studies on cell death and digestion in the foetal rat foot: the role of macrophages and hydrolytic enzymes. *J Cell Sci* 3:245-262
29. Mankin HJ (1964) Mitosis in articular cartilage of immature rabbits. A histologic, stathmokinetic (colchicine) and autoradiographic study. *Clin Orthop Relat Res* 34:170-183
30. Ito MM, Kida MY (2000) Morphological and biochemical re-evaluation of the process of cavitation in the rat knee joint: cellular and cell strata alterations in the interzone. *J Anat* 197 Pt 4:659-679
31. Lamb KJ, Lewthwaite JC, Lin JP, Simon D, Kavanagh E, Wheeler-Jones CP, Pitsillides AA (2003) Diverse range of fixed positional deformities and bone growth restraint provoked by flaccid paralysis in embryonic chicks. *Int J Exp Pathol* 84:191-199
32. Murray PD, Drachman DB (1969) The role of movement in the development of joints and related structures: the head and neck in the chick embryo. *J Embryol Exp Morphol* 22:349-371
33. Mitrovic D (1982) Development of the articular cavity in paralyzed chick embryos and in chick embryo limb buds cultured on chorioallantoic membranes. *Acta Anat (Basel)* 113:313-324
34. Osborne AC, Lamb KJ, Lewthwaite JC, Dowthwaite GP, Pitsillides AA (2002) Short-term rigid and flaccid paralyzes diminish growth of embryonic chick limbs and abrogate joint cavity formation but differentially preserve pre-cavitated joints. *J Musculoskelet Neuronal Interact* 2:448-456

- 1 35. Dowthwaite GP, Edwards JC, Pitsillides AA (1998) An essential role for the interaction
2 between hyaluronan and hyaluronan binding proteins during joint development. *J*
3 *Histochem Cytochem* 46:641-651
- 4 36. Archer CW, Dowthwaite GP, Francis-West P (2003) Development of synovial joints. *Birth*
5 *Defects Res C Embryo Today* 69:144-155
- 6 37. Giorgi M, Carriero A, Shefelbine SJ, Nowlan NC (2015) Effects of normal and abnormal
7 loading conditions on morphogenesis of the prenatal hip joint: application to hip dysplasia. *J*
8 *Biomech* 48:3390-3397
- 9 38. Ford CA, Nowlan NC, Thomopoulos S, Killian ML (2017) Effects of imbalanced muscle loading
10 on hip joint development and maturation. *J Orthop Res* 35:1128-1136
- 11 39. Brunt LH, Skinner RE, Roddy KA, Araujo NM, Rayfield EJ, Hammond CL (2016) Differential
12 effects of altered patterns of movement and strain on joint cell behaviour and skeletal
13 morphogenesis. *Osteoarthritis Cartilage* 24:1940-1950
- 14 40. Seo HS, Serra R (2007) Deletion of *Tgfb2* in *Prx1-cre* expressing mesenchyme results in
15 defects in development of the long bones and joints. *Dev Biol* 310:304-316
- 16 41. Jain L (2018) Hormonal Regulation of Human Development. *Clin Perinatol* 45:xiii-xv
- 17 42. Decker RS (2017) Articular cartilage and joint development from embryogenesis to
18 adulthood. *Semin Cell Dev Biol* 62:50-56
- 19 43. Harcke HT (1999) Developmental dysplasia of the hip: a spectrum of abnormality. *Pediatrics*
20 103:152
- 21 44. Loder RT, Skopelja EN (2011) The epidemiology and demographics of hip dysplasia. *ISRN*
22 *Orthop* 2011:238607
- 23 45. Bjerkreim I, van der Hagen CB (1974) Congenital dislocation of the hip joint in Norway. V.
24 Evaluation of genetic and environmental factors. *Clin Genet* 5:433-448
- 25 46. Li L, Sun K, Zhang L, Zhao Q, Cheng X, Dang Y (2013) Heritability and sibling recurrent risk of
26 developmental dysplasia of the hip in Chinese population. *Eur J Clin Invest* 43:589-594
- 27 47. Atasu M, Akkoyunlu U, Tokgozoglu N, Say B (1972) The heritability of liability to congenital
28 dislocation of the hip. *Turk J Pediatr* 14:23-26
- 29 48. Stevenson DA, Mineau G, Kerber RA, Viskochil DH, Schaefer C, Roach JW (2009) Familial
30 predisposition to developmental dysplasia of the hip. *J Pediatr Orthop* 29:463-466
- 31 49. Hatzikotoulas K, Roposch A, Consortium DDHCC, Shah KM, Clark MJ, Bratherton S, Limbani V,
32 Steinberg J, Zengini E, Warsame K, Ratnayake M, Tselepi M, Schwartzentruber J, Loughlin J,
33 Eastwood DM, Zeggini E, Wilkinson JM (2018) Genome-wide association study of
34 developmental dysplasia of the hip identifies an association with *GDF5*. *Commun Biol* 1:56
- 35 50. Yang J, Lee SH, Goddard ME, Visscher PM (2011) GCTA: a tool for genome-wide complex trait
36 analysis. *Am J Hum Genet* 88:76-82
- 37 51. Feldman G, Dalsey C, Fertala K, Azimi D, Fortina P, Devoto M, Pacifici M, Parvizi J (2010) The
38 Otto Aufranc Award: Identification of a 4 Mb region on chromosome 17q21 linked to
39 developmental dysplasia of the hip in one 18-member, multigeneration family. *Clin Orthop*
40 *Relat Res* 468:337-344
- 41 52. Mabuchi A, Nakamura S, Takatori Y, Ikegawa S (2006) Familial osteoarthritis of the hip joint
42 associated with acetabular dysplasia maps to chromosome 13q. *Am J Hum Genet* 79:163-
43 168
- 44 53. Watson CM, Crinnion LA, Gleghorn L, Newman WG, Ramesar R, Beighton P, Wallis GA (2015)
45 Identification of a mutation in the ubiquitin-fold modifier 1-specific peptidase 2 gene, *UFSP2*,
46 in an extended South African family with Beukes hip dysplasia. *S Afr Med J* 105:558-563
- 47 54. Imabayashi H, Mori T, Gojo S, Kiyono T, Sugiyama T, Irie R, Isogai T, Hata J, Toyama Y,
48 Umezawa A (2003) Redifferentiation of dedifferentiated chondrocytes and chondrogenesis
49 of human bone marrow stromal cells via chondrosphere formation with expression profiling
50 by large-scale cDNA analysis. *Exp Cell Res* 288:35-50

- 1
2
3
4
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6
7
8
9
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12
13
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16
17
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46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
55. Vetter K, Wurst W (2001) Expression of a novel mouse gene 'mbFZb' in distinct regions of the developing nervous system and the adult brain. *Mech Dev* 100:123-125
 56. Deng FY, Dong SS, Xu XH, Liu YJ, Liu YZ, Shen H, Tian Q, Li J, Deng HW (2013) Genome-wide association study identified UQCC locus for spine bone size in humans. *Bone* 53:129-133
 57. Sanna S, Jackson AU, Nagaraja R, Willer CJ, Chen WM, Bonnycastle LL, Shen H, Timpson N, Lettre G, Usala G, Chines PS, Stringham HM, Scott LJ, Dei M, Lai S, Albai G, Crisponi L, Naitza S, Doheny KF, Pugh EW, Ben-Shlomo Y, Ebrahim S, Lawlor DA, Bergman RN, Watanabe RM, Uda M, Tuomilehto J, Coresh J, Hirschhorn JN, Shuldiner AR, Schlessinger D, Collins FS, Davey Smith G, Boerwinkle E, Cao A, Boehnke M, Abecasis GR, Mohlke KL (2008) Common variants in the GDF5-UQCC region are associated with variation in human height. *Nat Genet* 40:198-203
 58. Soranzo N, Rivadeneira F, Chinappen-Horsley U, Malkina I, Richards JB, Hammond N, Stolk L, Nica A, Inouye M, Hofman A, Stephens J, Wheeler E, Arp P, Gwilliam R, Jhamai PM, Potter S, Chaney A, Ghorri MJ, Ravindrarajah R, Ermakov S, Estrada K, Pols HA, Williams FM, McArdle WL, van Meurs JB, Loos RJ, Dermitzakis ET, Ahmadi KR, Hart DJ, Ouweland WH, Wareham NJ, Barroso I, Sandhu MS, Strachan DP, Livshits G, Spector TD, Uitterlinden AG, Deloukas P (2009) Meta-analysis of genome-wide scans for human adult stature identifies novel Loci and associations with measures of skeletal frame size. *PLoS Genet* 5:e1000445
 59. Borkakoti N (1998) Matrix metalloproteases: variations on a theme. *Prog Biophys Mol Biol* 70:73-94
 60. Fontenele EG, Moraes ME, d'Alva CB, Pinheiro DP, Landim SA, Barros FA, Trarbach EB, Mendonca BB, Jorge AA (2015) Association Study of GWAS-Derived Loci with Height in Brazilian Children: Importance of MAP3K3, MMP24 and IGF1R Polymorphisms for Height Variation. *Horm Res Paediatr* 84:248-253
 61. Zhao J, Li M, Bradfield JP, Zhang H, Mentch FD, Wang K, Sleiman PM, Kim CE, Glessner JT, Hou C, Keating BJ, Thomas KA, Garris ML, Deliard S, Frackelton EC, Otieno FG, Chiavacci RM, Berkowitz RI, Hakonarson H, Grant SF (2010) The role of height-associated loci identified in genome wide association studies in the determination of pediatric stature. *BMC Med Genet* 11:96
 62. Moise AR, Kuksa V, Imanishi Y, Palczewski K (2004) Identification of all-trans-retinol:all-trans-13,14-dihydroretinol saturase. *J Biol Chem* 279:50230-50242
 63. Ross SA, McCaffery PJ, Drager UC, De Luca LM (2000) Retinoids in embryonal development. *Physiol Rev* 80:1021-1054
 64. Loder RT, Skopelja EN (2011) The epidemiology and demographics of legg-calve-perthes' disease. *ISRN Orthop* 2011:504393
 65. Hall DJ (1986) Genetic aspects of Perthes' disease. A critical review. *Clin Orthop Relat Res*:100-114
 66. Metcalfe D, Van Dijck S, Parsons N, Christensen K, Perry DC (2016) A Twin Study of Perthes Disease. *Pediatrics* 137:e20153542
 67. Woratanarat P, Thaveeratitharm C, Woratanarat T, Angsanuntsukh C, Attia J, Thakkinstian A (2014) Meta-analysis of hypercoagulability genetic polymorphisms in Perthes disease. *J Orthop Res* 32:1-7
 68. Loder RT, Skopelja EN (2011) The epidemiology and demographics of slipped capital femoral epiphysis. *ISRN Orthop* 2011:486512
 69. Rennie AM (1982) The inheritance of slipped upper femoral epiphysis. *J Bone Joint Surg Br* 64:180-184
 70. Witbreuk M, van Kemenade FJ, van der Sluijs JA, Jansma EP, Rotteveel J, van Royen BJ (2013) Slipped capital femoral epiphysis and its association with endocrine, metabolic and chronic diseases: a systematic review of the literature. *J Child Orthop* 7:213-223

- 1 71. Ito K, Minka MA, 2nd, Leunig M, Werlen S, Ganz R (2001) Femoroacetabular impingement
2 and the cam-effect. A MRI-based quantitative anatomical study of the femoral head-neck
3 offset. *J Bone Joint Surg Br* 83:171-176
- 4 72. Ganz R, Parvizi J, Beck M, Leunig M, Notzli H, Siebenrock KA (2003) Femoroacetabular
5 impingement: a cause for osteoarthritis of the hip. *Clin Orthop Relat Res*:112-120
- 6 73. Beck M, Kalhor M, Leunig M, Ganz R (2005) Hip morphology influences the pattern of
7 damage to the acetabular cartilage: femoroacetabular impingement as a cause of early
8 osteoarthritis of the hip. *J Bone Joint Surg Br* 87:1012-1018
- 9 74. Agricola R, Bessems JH, Ginai AZ, Heijboer MP, van der Heijden RA, Verhaar JA, Weinans H,
10 Waarsing JH (2012) The development of Cam-type deformity in adolescent and young male
11 soccer players. *Am J Sports Med* 40:1099-1106
- 12 75. van Klij P, Heerey J, Waarsing JH, Agricola R (2018) The Prevalence of Cam and Pincer
13 Morphology and Its Association With Development of Hip Osteoarthritis. *J Orthop Sports
14 Phys Ther* 48:230-238
- 15 76. Laborie LB, Lehmann TG, Engesaeter IO, Eastwood DM, Engesaeter LB, Rosendahl K (2011)
16 Prevalence of radiographic findings thought to be associated with femoroacetabular
17 impingement in a population-based cohort of 2081 healthy young adults. *Radiology* 260:494-
18 502
- 19 77. Laborie LB, Lehmann TG, Engesaeter IO, Engesaeter LB, Rosendahl K (2013) Is a positive
20 femoroacetabular impingement test a common finding in healthy young adults? *Clin Orthop
21 Relat Res* 471:2267-2277
- 22 78. Laborie LB, Lehmann TG, Engesaeter IO, Sera F, Engesaeter LB, Rosendahl K (2014) The alpha
23 angle in cam-type femoroacetabular impingement: new reference intervals based on 2038
24 healthy young adults. *Bone Joint J* 96-B:449-454
- 25 79. van Klij P, Heijboer MP, Ginai AZ, Verhaar JAN, Waarsing JH, Agricola R (2019) Cam
26 morphology in young male football players mostly develops before proximal femoral growth
27 plate closure: a prospective study with 5-year follow-up. *Br J Sports Med* 53:532-538
- 28 80. Pollard TC, Batra RN, Judge A, Watkins B, McNally EG, Gill HS, Thomas GE, Glyn-Jones S,
29 Arden NK, Carr AJ (2013) The hereditary predisposition to hip osteoarthritis and its
30 association with abnormal joint morphology. *Osteoarthritis Cartilage* 21:314-321
- 31 81. Heimann T, Meinzer HP (2009) Statistical shape models for 3D medical image segmentation:
32 a review. *Med Image Anal* 13:543-563
- 33 82. Yokota F, Okada T, Takao M, Sugano N, Tada Y, Sato Y (2009) Automated segmentation of
34 the femur and pelvis from 3D CT data of diseased hip using hierarchical statistical shape
35 model of joint structure. *Med Image Comput Comput Assist Interv* 12:811-818
- 36 83. Lindner C, Thiagarajah S, Wilkinson JM, arc OC, Wallis GA, Cootes TF (2013) Development of
37 a fully automatic shape model matching (FASMM) system to derive statistical shape models
38 from radiographs: application to the accurate capture and global representation of proximal
39 femur shape. *Osteoarthritis Cartilage* 21:1537-1544
- 40 84. Lindner C, Thiagarajah S, Wilkinson JM, Wallis GA, Cootes TF, arc OC (2013) Accurate bone
41 segmentation in 2D radiographs using fully automatic shape model matching based on
42 regression-voting. *Med Image Comput Comput Assist Interv* 16:181-189
- 43 85. Fitzpatrick CK, Baldwin MA, Laz PJ, FitzPatrick DP, Lerner AL, Rullkoetter PJ (2011)
44 Development of a statistical shape model of the patellofemoral joint for investigating
45 relationships between shape and function. *J Biomech* 44:2446-2452
- 46 86. Van Haver A, Mahieu P, Claessens T, Li H, Pattyn C, Verdonk P, Audenaert EA (2014) A
47 statistical shape model of trochlear dysplasia of the knee. *Knee* 21:518-523
- 48 87. Padoia V, Lansdown DA, Zaid M, McCulloch CE, Souza R, Ma CB, Li X (2015) Three-
49 dimensional MRI-based statistical shape model and application to a cohort of knees with
50 acute ACL injury. *Osteoarthritis Cartilage* 23:1695-1703

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2
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4
5
6
7
8
9
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14
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16
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46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
88. Khanduja V, Baelde N, Dobbelaere A, Van Houcke J, Li H, Pattyn C, Audenaert EA (2016) Patient-specific assessment of dysmorphism of the femoral head-neck junction: a statistical shape model approach. *Int J Med Robot* 12:765-772
 89. Baird DA, Evans DS, Kamanu FK, Gregory JS, Saunders FR, Giuraniuc CV, Barr RJ, Aspden RM, Jenkins D, Kiel DP, Orwoll ES, Cummings SR, Lane NE, Mullin BH, Williams FM, Richards JB, Wilson SG, Spector TD, Faber BG, Lawlor DA, Grundberg E, Ohlsson C, Pettersson-Kymmer U, Capellini TD, Richard D, Beck TJ, Evans DM, Paternoster L, Karasik D, Tobias JH (2019) Identification of Novel Loci Associated With Hip Shape: A Meta-Analysis of Genomewide Association Studies. *J Bone Miner Res* 34:241-251
 90. Hsu YH, Estrada K, Evangelou E, Ackert-Bicknell C, Akesson K, Beck T, Brown SJ, Capellini T, Carbone L, Cauley J, Cheung CL, Cummings SR, Czerwinski S, Demissie S, Econs M, Evans D, Farber C, Gautvik K, Harris T, Kammerer C, Kemp J, Koller DL, Kung A, Lawlor D, Lee M, Lorentzon M, McGuigan F, Medina-Gomez C, Mitchell B, Newman A, Nielson C, Ohlsson C, Peacock M, Reppe S, Richards JB, Robbins J, Sigurdsson G, Spector TD, Stefansson K, Streeten E, Styrkarsdottir U, Tobias J, Trajanoska K, Uitterlinden A, Vandenput L, Wilson SG, Yerges-Armstrong L, Young M, Zillikens MC, Rivadeneira F, Kiel DP, Karasik D (2019) Meta-Analysis of Genomewide Association Studies Reveals Genetic Variants for Hip Bone Geometry. *J Bone Miner Res* 34:1284-1296
 91. Zheng J, Erzurumluoglu AM, Elsworth BL, Kemp JP, Howe L, Haycock PC, Hemani G, Tansey K, Laurin C, Early G, Lifecourse Epidemiology Eczema C, Pourcain BS, Warrington NM, Finucane HK, Price AL, Bulik-Sullivan BK, Anttila V, Paternoster L, Gaunt TR, Evans DM, Neale BM (2017) LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. *Bioinformatics* 33:272-279
 92. Styrkarsdottir U, Stefansson OA, Gunnarsdottir K, Thorleifsson G, Lund SH, Stefansdottir L, Juliusson K, Agustsdottir AB, Zink F, Halldorsson GH, Ivarsdottir EV, Benonisdottir S, Jonsson H, Gylfason A, Norland K, Trajanoska K, Boer CG, Southam L, Leung JCS, Tang NLS, Kwok TCY, Lee JSW, Ho SC, Byrjalsen I, Center JR, Lee SH, Koh JM, Lohmander LS, Ho-Pham LT, Nguyen TV, Eisman JA, Woo J, Leung PC, Loughlin J, Zeggini E, Christiansen C, Rivadeneira F, van Meurs J, Uitterlinden AG, Mogensen B, Jonsson H, Ingvarsson T, Sigurdsson G, Benediktsson R, Sulem P, Jonsdottir I, Masson G, Holm H, Norddahl GL, Thorsteinsdottir U, Gudbjartsson DF, Stefansson K (2019) GWAS of bone size yields twelve loci that also affect height, BMD, osteoarthritis or fractures. *Nat Commun* 10:2054
 93. Lehmann TG, Engesaeter IO, Laborie LB, Lie SA, Rosendahl K, Engesaeter LB (2012) Total hip arthroplasty in young adults, with focus on Perthes' disease and slipped capital femoral epiphysis: follow-up of 540 subjects reported to the Norwegian Arthroplasty Register during 1987-2007. *Acta Orthop* 83:159-164
 94. Wiberg G (1939) Studies on Dysplastic Acetabula and Congenital Subluxation of the Hip Joint with Special References to the Complication of Osteoarthritis. *Acta Chir Scand* 83:1-135
 95. Cooperman DR, Wallensten R, Stulberg SD (1983) Acetabular dysplasia in the adult. *Clin Orthop Relat Res*:79-85
 96. McWilliams DF, Doherty SA, Jenkins WD, Maciewicz RA, Muir KR, Zhang W, Doherty M (2010) Mild acetabular dysplasia and risk of osteoarthritis of the hip: a case-control study. *Ann Rheum Dis* 69:1774-1778
 97. Murray RO (1965) The aetiology of primary osteoarthritis of the hip. *Br J Radiol* 38:810-824
 98. Solomon L (1976) Patterns of osteoarthritis of the hip. *Journal of Bone & Joint Surgery - British Volume* 58:176-183
 99. Harris WH (1986) Etiology of osteoarthritis of the hip. *Clin Orthop Relat Res*:20-33
 100. Ganz R, Leunig M, Leunig-Ganz K, Harris WH (2008) The etiology of osteoarthritis of the hip: an integrated mechanical concept. *Clin Orthop Relat Res* 466:264-272

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9
10
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47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
101. Doherty M, Courtney P, Doherty S, Jenkins W, Maciewicz RA, Muir K, Zhang W (2008) Nonspherical femoral head shape (pistol grip deformity), neck shaft angle, and risk of hip osteoarthritis: a case-control study. *Arthritis Rheum* 58:3172-3182
 102. Kim YH (1989) Relationship between the sphericity of femoral head-acetabulum and the low incidence of primary osteoarthritis of the hip joint in Koreans. *Yonsei Med J* 30:280-287
 103. Dudda M, Kim YJ, Zhang Y, Nevitt MC, Xu L, Niu J, Goggins J, Doherty M, Felson DT (2011) Morphologic differences between the hips of Chinese women and white women: could they account for the ethnic difference in the prevalence of hip osteoarthritis? *Arthritis Rheum* 63:2992-2999
 104. Edwards K, Leyland KM, Sanchez-Santos MT, Arden CP, Spector TD, Nelson AE, Jordan JM, Nevitt M, Hunter DJ, Arden NK (2019) Differences between race and sex in measures of hip morphology: a population-based comparative study. *Osteoarthritis Cartilage*
 105. Hoaglund FT (2013) Primary osteoarthritis of the hip: a genetic disease caused by European genetic variants. *J Bone Joint Surg Am* 95:463-468
 106. Nicholls AS, Kiran A, Pollard TC, Hart DJ, Arden CP, Spector T, Gill HS, Murray DW, Carr AJ, Arden NK (2011) The association between hip morphology parameters and nineteen-year risk of end-stage osteoarthritis of the hip: a nested case-control study. *Arthritis Rheum* 63:3392-3400
 107. Thomas GE, Palmer AJ, Batra RN, Kiran A, Hart D, Spector T, Javaid MK, Judge A, Murray DW, Carr AJ, Arden NK, Glyn-Jones S (2014) Subclinical deformities of the hip are significant predictors of radiographic osteoarthritis and joint replacement in women. A 20 year longitudinal cohort study. *Osteoarthritis Cartilage* 22:1504-1510
 108. Agricola R, Heijboer MP, Bierma-Zeinstra SM, Verhaar JA, Weinans H, Waarsing JH (2013) Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK). *Ann Rheum Dis* 72:918-923
 109. Agricola R, Heijboer MP, Roze RH, Reijman M, Bierma-Zeinstra SM, Verhaar JA, Weinans H, Waarsing JH (2013) Pincer deformity does not lead to osteoarthritis of the hip whereas acetabular dysplasia does: acetabular coverage and development of osteoarthritis in a nationwide prospective cohort study (CHECK). *Osteoarthritis Cartilage* 21:1514-1521
 110. Waarsing JH, Rozendaal RM, Verhaar JA, Bierma-Zeinstra SM, Weinans H (2010) A statistical model of shape and density of the proximal femur in relation to radiological and clinical OA of the hip. *Osteoarthritis Cartilage* 18:787-794
 111. Castano-Betancourt MC, Van Meurs JB, Bierma-Zeinstra S, Rivadeneira F, Hofman A, Weinans H, Uitterlinden AG, Waarsing JH (2013) The contribution of hip geometry to the prediction of hip osteoarthritis. *Osteoarthritis Cartilage* 21:1530-1536
 112. Agricola R, Leyland KM, Bierma-Zeinstra SM, Thomas GE, Emans PJ, Spector TD, Weinans H, Waarsing JH, Arden NK (2015) Validation of statistical shape modelling to predict hip osteoarthritis in females: data from two prospective cohort studies (Cohort Hip and Cohort Knee and Chingford). *Rheumatology (Oxford)* 54:2033-2041
 113. Baker-Lepain JC, Lynch JA, Parimi N, McCulloch CE, Nevitt MC, Corr M, Lane NE (2012) Variant alleles of the Wnt antagonist FRZB are determinants of hip shape and modify the relationship between hip shape and osteoarthritis. *Arthritis Rheum* 64:1457-1465
 114. Panoutsopoulou K, Southam L, Elliott KS, Wrayner N, Zhai G, Beazley C, Thorleifsson G, Arden NK, Carr A, Chapman K, Deloukas P, Doherty M, McCaskie A, Ollier WE, Ralston SH, Spector TD, Valdes AM, Wallis GA, Wilkinson JM, Arden E, Battley K, Blackburn H, Blanco FJ, Bumpstead S, Cupples LA, Day-Williams AG, Dixon K, Doherty SA, Esko T, Evangelou E, Felson D, Gomez-Reino JJ, Gonzalez A, Gordon A, Gwilliam R, Halldorsson BV, Hauksson VB, Hofman A, Hunt SE, Ioannidis JP, Ingvarsson T, Jonsdottir I, Jonsson H, Keen R, Kerkhof HJ, Kloppenburg MG, Koller N, Lakenberg N, Lane NE, Lee AT, Metspalu A, Meulenbelt I, Nevitt MC, O'Neill F, Parimi N, Potter SC, Rego-Perez I, Riancho JA, Sherburn K, Slagboom PE, Stefansson K, Stykarsdottir U, Sumillera M, Swift D, Thorsteinsdottir U, Tsezou A,

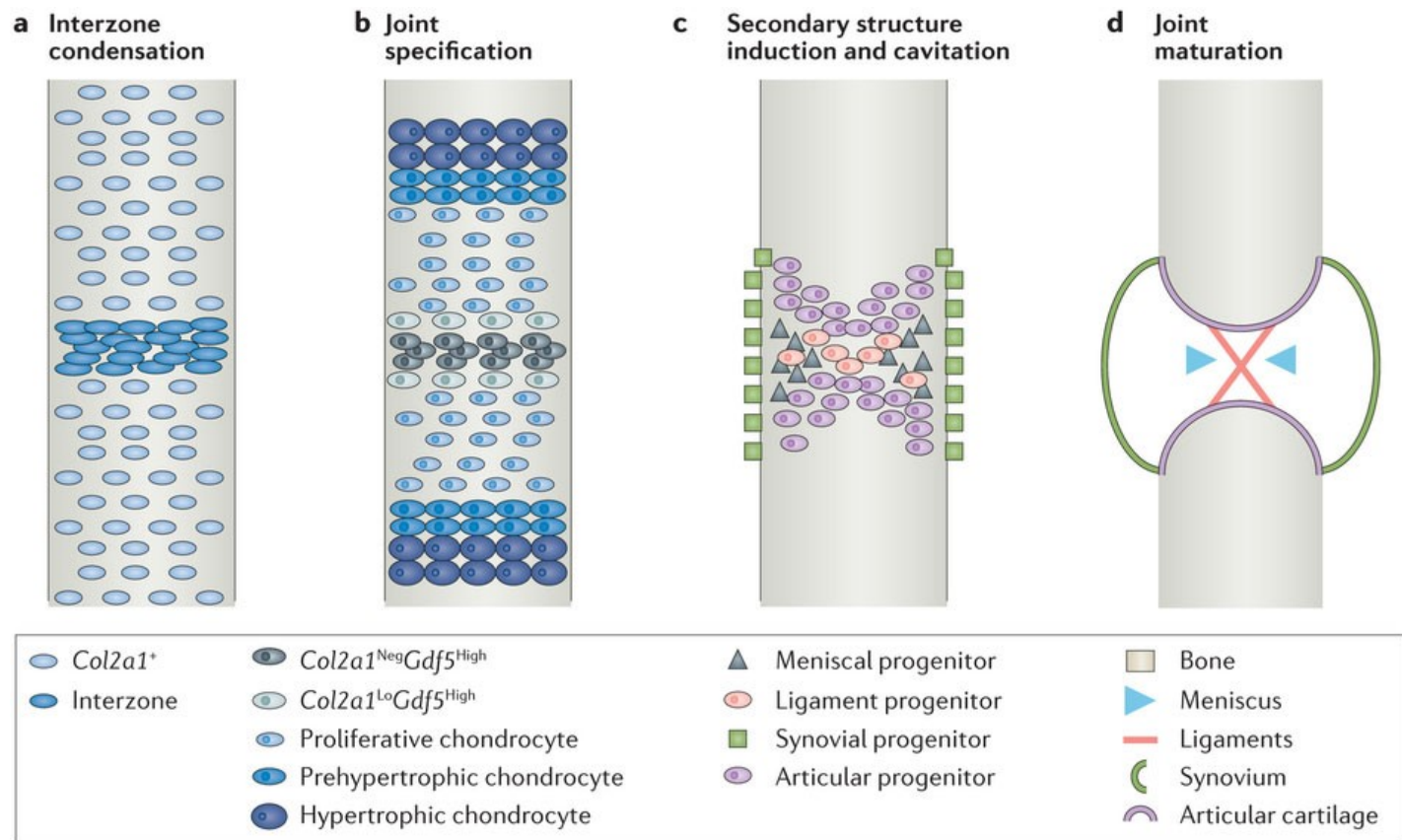
- 1 Uitterlinden AG, van Meurs JB, Watkins B, Wheeler M, Mitchell S, Zhu Y, Zmuda JM, Zeggini
2 E, Loughlin J (2011) Insights into the genetic architecture of osteoarthritis from stage 1 of
3 the arcOGEN study. *Ann Rheum Dis* 70:864-867
- 4 115. Lindner C, Thiagarajah S, Wilkinson JM, Panoutsopoulou K, Day-Williams AG, arc OC, Cootes
5 TF, Wallis GA (2015) Investigation of association between hip osteoarthritis susceptibility loci
6 and radiographic proximal femur shape. *Arthritis Rheumatol* 67:2076-2084
- 7 116. Haverkamp DJ, Schiphof D, Bierma-Zeinstra SM, Weinans H, Waarsing JH (2011) Variation in
8 joint shape of osteoarthritic knees. *Arthritis Rheum* 63:3401-3407
- 9 117. Wise BL, Niu J, Zhang Y, Liu F, Pang J, Lynch JA, Lane NE (2018) Bone shape mediates the
10 relationship between sex and incident knee osteoarthritis. *BMC Musculoskelet Disord*
11 19:331
- 12 118. Gregory JS, Waarsing JH, Day J, Pols HA, Reijman M, Weinans H, Aspden RM (2007) Early
13 identification of radiographic osteoarthritis of the hip using an active shape model to
14 quantify changes in bone morphometric features: can hip shape tell us anything about the
15 progression of osteoarthritis? *Arthritis Rheum* 56:3634-3643
- 16 119. Hunter D, Nevitt M, Lynch J, Kraus VB, Katz JN, Collins JE, Bowes M, Guermazi A, Roemer FW,
17 Losina E, Consortium FOB (2016) Longitudinal validation of periarticular bone area and 3D
18 shape as biomarkers for knee OA progression? Data from the FNIH OA Biomarkers
19 Consortium. *Ann Rheum Dis* 75:1607-1614
- 20 120. Blake GM, Wahner HW, Fogelman I (1999) Technical principals of x-ray absorptiometry. In:
21 Blake GM, Wahner HW, Fogelman I (eds) *The evaluation of osteoporosis: Dual energy x-ray
22 absorptiometry and ultrasound in clinical practice*. Martin Dunitz Ltd, London, p 45-71
- 23 121. Inamdar G, Pedoia V, Rossi-Devries J, Samaan MA, Link TM, Souza RB, Majumdar S (2019)
24 MR study of longitudinal variations in proximal femur 3D morphological shape and
25 associations with cartilage health in hip osteoarthritis. *J Orthop Res* 37:161-170
- 26 122. Bombelli R (1983) *Osteoarthritis of the hip: classification and pathogenesis*. Springer-Verlag,
27 Berlin
- 28 123. Panoutsopoulou K, Thiagarajah S, Zengini E, Day-Williams AG, Ramos YF, Meessen JM,
29 Huetink K, Nelissen RG, Southam L, Rayner NW, arc OC, Doherty M, Meulenbelt I, Zeggini E,
30 Wilkinson JM (2016) Radiographic endophenotyping in hip osteoarthritis improves the
31 precision of genetic association analysis. *Ann Rheum Dis*
- 32 124. Zengini E, Hatzikotoulas K, Tachmazidou I, Steinberg J, Hartwig FP, Southam L, Hackinger S,
33 Boer CG, Styrkarsdottir U, Gilly A, Suveges D, Killian B, Ingvarsson T, Jonsson H, Babis GC,
34 McCaskie A, Uitterlinden AG, van Meurs JBJ, Thorsteinsdottir U, Stefansson K, Davey Smith
35 G, Wilkinson JM, Zeggini E (2018) Genome-wide analyses using UK Biobank data provide
36 insights into the genetic architecture of osteoarthritis. *Nat Genet*
- 37 125. Tachmazidou I, Hatzikotoulas K, Southam L, Esparza-Gordillo J, Haberland V, Zheng J,
38 Johnson T, Koprulu M, Zengini E, Steinberg J, Wilkinson JM, Bhatnagar S, Hoffman JD,
39 Buchan N, Süveges D, Yerges-Armstrong L, Smith GD, Gaunt TR, Scott RA, McCarthy LC,
40 Zeggini E, arc OC (2019) Identification of new therapeutic targets for osteoarthritis through
41 genome-wide analyses of UK Biobank data. *Nature Genetics*
- 42 126. Styrkarsdottir U, Helgason H, Sigurdsson A, Norddahl GL, Agustsdottir AB, Reynard LN,
43 Villalvilla A, Halldorsson GH, Jonasdottir A, Magnusdottir A, Oddson A, Sulem G, Zink F,
44 Sveinbjornsson G, Helgason A, Johannsdottir HS, Helgadottir A, Stefansson H, Gretarsdottir
45 S, Rafnar T, Almdahl IS, Braekhus A, Fladby T, Selbaek G, Hosseinpanah F, Azizi F, Koh JM,
46 Tang NLS, Daneshpour MS, Mayordomo JI, Welt C, Braund PS, Samani NJ, Kiemeny LA,
47 Lohmander LS, Christiansen C, Andreassen OA, arc Oc, Magnusson O, Masson G, Kong A,
48 Jonsdottir I, Gudbjartsson D, Sulem P, Jonsson H, Loughlin J, Ingvarsson T, Thorsteinsdottir U,
49 Stefansson K (2017) Whole-genome sequencing identifies rare genotypes in COMP and
50 CHADL associated with high risk of hip osteoarthritis. *Nat Genet* 49:801-805
- 51
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56
57
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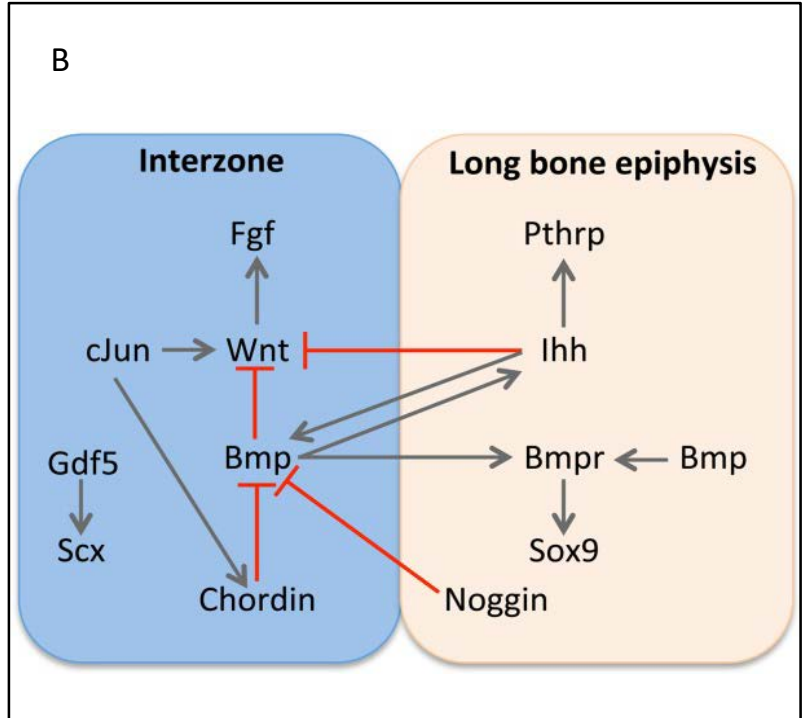
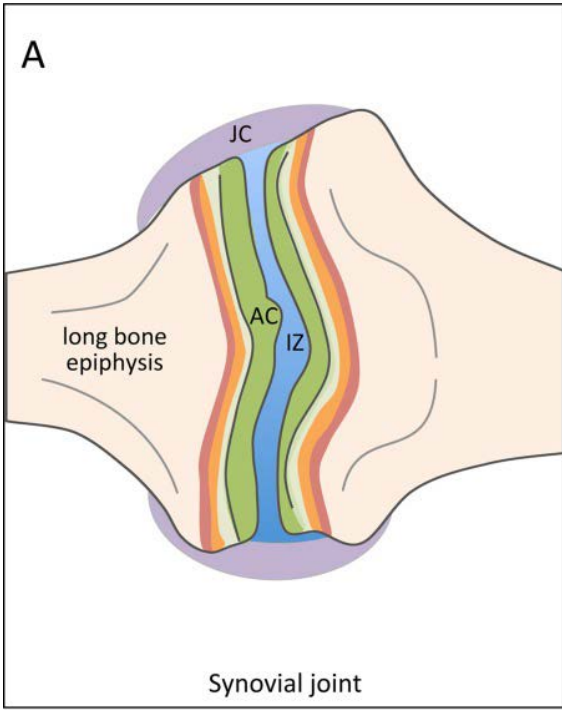
127. Styrkarsdottir U, Lund SH, Thorleifsson G, Zink F, Stefansson OA, Sigurdsson JK, Juliusson K, Bjarnadottir K, Sigurbjornsdottir S, Jonsson S, Norland K, Stefansdottir L, Sigurdsson A, Sveinbjornsson G, Oddsson A, Bjornsdottir G, Gudmundsson RL, Halldorsson GH, Rafnar T, Jonsdottir I, Steingrimsson E, Norddahl GL, Masson G, Sulem P, Jonsson H, Ingvarsson T, Gudbjartsson DF, Thorsteinsdottir U, Stefansson K (2018) Meta-analysis of Icelandic and UK data sets identifies missense variants in SMO, IL11, COL11A1 and 13 more new loci associated with osteoarthritis. *Nat Genet* 50:1681-1687
128. arcOGEN Consortium; arcOGEN Collaborators ZE, Panoutsopoulou K, Southam L, Rayner NW, Day-Williams AG, Lopes MC, Boraska V, Esko T, Evangelou E, Hoffman A, Houwing-Duistermaat JJ, Ingvarsson T, Jonsdottir I, Jonsson H, Kerkhof HJ, Kloppenburg M, Bos SD, Mangino M, Metrustry S, Slagboom PE, Thorleifsson G, Raine EV, Ratnayake M, Ricketts M, Beazley C, Blackburn H, Bumpstead S, Elliott KS, Hunt SE, Potter SC, Shin SY, Yadav VK, Zhai G, Sherburn K, Dixon K, Arden E, Aslam N, Battley PK, Carluke I, Doherty S, Gordon A, Joseph J, Keen R, Koller NC, Mitchell S, O'Neill F, Paling E, Reed MR, Rivadeneira F, Swift D, Walker K, Watkins B, Wheeler M, Birrell F, Ioannidis JP, Meulenbelt I, Metspalu A, Rai A, Salter D, Stefansson K, Styrkarsdottir U, Uitterlinden AG, van Meurs JB, Chapman K, Deloukas P, Ollier WE, Wallis GA, Arden N, Carr A, Doherty M, McCaskie A, Wilkinson JM, Ralston SH, Valdes AM, Spector TD, Loughlin J. (2012) Identification of new susceptibility loci for osteoarthritis (arcOGEN): a genome-wide association study. *Lancet* 380:815-823
129. Reynard LN, Barter MJ (2019) Osteoarthritis Year in Review 2019: Genetics, Genomics and Epigenetics. *Osteoarthritis Cartilage*
130. Miyamoto Y, Mabuchi A, Shi D, Kubo T, Takatori Y, Saito S, Fujioka M, Sudo A, Uchida A, Yamamoto S, Ozaki K, Takigawa M, Tanaka T, Nakamura Y, Jiang Q, Ikegawa S (2007) A functional polymorphism in the 5' UTR of GDF5 is associated with susceptibility to osteoarthritis. *Nat Genet* 39:529-533
131. Miyamoto Y, Shi D, Nakajima M, Ozaki K, Sudo A, Kotani A, Uchida A, Tanaka T, Fukui N, Tsunoda T, Takahashi A, Nakamura Y, Jiang Q, Ikegawa S (2008) Common variants in DVWA on chromosome 3p24.3 are associated with susceptibility to knee osteoarthritis. *Nat Genet* 40:994-998
132. Nakajima M, Takahashi A, Kou I, Rodriguez-Fontenla C, Gomez-Reino JJ, Furuichi T, Dai J, Sudo A, Uchida A, Fukui N, Kubo M, Kamatani N, Tsunoda T, Malizos KN, Tsezou A, Gonzalez A, Nakamura Y, Ikegawa S (2010) New sequence variants in HLA class II/III region associated with susceptibility to knee osteoarthritis identified by genome-wide association study. *PLoS one* 5:e9723
133. Kerkhof HJ, Lories RJ, Meulenbelt I, Jonsdottir I, Valdes AM, Arp P, Ingvarsson T, Jhamai M, Jonsson H, Stolk L, Thorleifsson G, Zhai G, Zhang F, Zhu Y, van der Breggen R, Carr A, Doherty M, Doherty S, Felson DT, Gonzalez A, Halldorsson BV, Hart DJ, Hauksson VB, Hofman A, Ioannidis JP, Kloppenburg M, Lane NE, Loughlin J, Luyten FP, Nevitt MC, Parimi N, Pols HA, Rivadeneira F, Slagboom EP, Styrkarsdottir U, Tsezou A, van de Putte T, Zmuda J, Spector TD, Stefansson K, Uitterlinden AG, van Meurs JB (2010) A genome-wide association study identifies an osteoarthritis susceptibility locus on chromosome 7q22. *Arthritis Rheum* 62:499-510
134. Evangelou E, Valdes AM, Kerkhof HJ, Styrkarsdottir U, Zhu Y, Meulenbelt I, Lories RJ, Karassa FB, Tylianowski P, Bos SD, Akune T, Arden NK, Carr A, Chapman K, Cupples LA, Dai J, Deloukas P, Doherty M, Doherty S, Engstrom G, Gonzalez A, Halldorsson BV, Hammond CL, Hart DJ, Helgadottir H, Hofman A, Ikegawa S, Ingvarsson T, Jiang Q, Jonsson H, Kaprio J, Kawaguchi H, Kisand K, Kloppenburg M, Kujala UM, Lohmander LS, Loughlin J, Luyten FP, Mabuchi A, McCaskie A, Nakajima M, Nilsson PM, Nishida N, Ollier WE, Panoutsopoulou K, van de Putte T, Ralston SH, Rivadeneira F, Saarela J, Schulte-Merker S, Shi D, Slagboom PE, Sudo A, Tamm A, Thorleifsson G, Thorsteinsdottir U, Tsezou A, Wallis GA, Wilkinson JM, Yoshimura N, Zeggini E, Zhai G, Zhang F, Jonsdottir I, Uitterlinden AG, Felson DT, van Meurs

- 1 JB, Stefansson K, Ioannidis JP, Spector TD (2011) Meta-analysis of genome-wide association
2 studies confirms a susceptibility locus for knee osteoarthritis on chromosome 7q22. *Ann*
3 *Rheum Dis* 70:349-355
- 4 135. Day-Williams AG, Southam L, Panoutsopoulou K, Rayner NW, Esko T, Estrada K, Helgadóttir
5 HT, Hofman A, Ingvarsson T, Jonsson H, Keis A, Kerkhof HJ, Thorleifsson G, Arden NK, Carr A,
6 Chapman K, Deloukas P, Loughlin J, McCaskie A, Ollier WE, Ralston SH, Spector TD, Wallis
7 GA, Wilkinson JM, Aslam N, Birell F, Carluke I, Joseph J, Rai A, Reed M, Walker K, Doherty SA,
8 Jonsdóttir I, Maciewicz RA, Muir KR, Metspalu A, Rivadeneira F, Stefansson K, Styrkarsdóttir
9 U, Uitterlinden AG, van Meurs JB, Zhang W, Valdes AM, Doherty M, Zeggini E (2011) A
10 Variant in MCF2L Is Associated with Osteoarthritis. *Am J Hum Genet*
- 11 136. Evangelou E, Valdes AM, Castano-Betancourt MC, Doherty M, Doherty S, Esko T, Ingvarsson
12 T, Ioannidis JP, Kloppenburg M, Metspalu A, Ntzani EE, Panoutsopoulou K, Slagboom PE,
13 Southam L, Spector TD, Styrkarsdóttir U, Stefansson K, Uitterlinden AG, Wheeler M, Zeggini E,
14 Meulenbelt I, van Meurs JB, arcOgen consortium tT-OAc (2013) The DOT1L rs12982744
15 polymorphism is associated with osteoarthritis of the hip with genome-wide statistical
16 significance in males. *Ann Rheum Dis* 72:1264-1265
- 17 137. Styrkarsdóttir U, Thorleifsson G, Helgadóttir HT, Bomer N, Metrustry S, Bierma-Zeinstra S,
18 Strijbosch AM, Evangelou E, Hart D, Beekman M, Jonasdóttir A, Sigurdsson A, Eiriksson FF,
19 Thorsteinsdóttir M, Frigge ML, Kong A, Gudjonsson SA, Magnusson OT, Masson G,
20 Consortium T-O, arc OC, Hofman A, Arden NK, Ingvarsson T, Lohmander S, Kloppenburg M,
21 Rivadeneira F, Nelissen RG, Spector T, Uitterlinden A, Slagboom PE, Thorsteinsdóttir U,
22 Jonsdóttir I, Valdes AM, Meulenbelt I, van Meurs J, Jonsson H, Stefansson K (2014) Severe
23 osteoarthritis of the hand associates with common variants within the ALDH1A2 gene and
24 with rare variants at 1p31. *Nat Genet* 46:498-502
- 25 138. Evangelou E, Kerkhof HJ, Styrkarsdóttir U, Ntzani EE, Bos SD, Esko T, Evans DS, Metrustry S,
26 Panoutsopoulou K, Ramos YF, Thorleifsson G, Tsilidis KK, arc OC, Arden N, Aslam N, Bellamy
27 N, Birrell F, Blanco FJ, Carr A, Chapman K, Day-Williams AG, Deloukas P, Doherty M,
28 Engstrom G, Helgadóttir HT, Hofman A, Ingvarsson T, Jonsson H, Keis A, Keurentjes JC,
29 Kloppenburg M, Lind PA, McCaskie A, Martin NG, Milani L, Montgomery GW, Nelissen RG,
30 Nevitt MC, Nilsson PM, Ollier WE, Parimi N, Rai A, Ralston SH, Reed MR, Riancho JA,
31 Rivadeneira F, Rodriguez-Fontenla C, Southam L, Thorsteinsdóttir U, Tsezou A, Wallis GA,
32 Wilkinson JM, Gonzalez A, Lane NE, Lohmander LS, Loughlin J, Metspalu A, Uitterlinden AG,
33 Jonsdóttir I, Stefansson K, Slagboom PE, Zeggini E, Meulenbelt I, Ioannidis JP, Spector TD, van
34 Meurs JB, Valdes AM (2014) A meta-analysis of genome-wide association studies identifies
35 novel variants associated with osteoarthritis of the hip. *Ann Rheum Dis* 73:2130-2136
- 36 139. Hackinger S, Trajanoska K, Styrkarsdóttir U, Zeggini E, Steinberg J, Ritchie GRS, Hatzikotoulas
37 K, Gilly A, Evangelou E, Kemp JP, arcOgen Consortium GC, Evans D, Ingvarsson T, Jonsson H,
38 Thorsteinsdóttir U, Stefansson K, McCaskie AW, Brooks RA, Wilkinson JM, Rivadeneira F,
39 Zeggini E (2017) Evaluation of shared genetic aetiology between osteoarthritis and bone
40 mineral density identifies SMAD3 as a novel osteoarthritis risk locus. *Hum Mol Genet*
41 26:3850-3858
- 42 140. Liu Y, Yau MS, Yerges-Armstrong LM, Duggan DJ, Renner JB, Hochberg MC, Mitchell BD,
43 Jackson RD, Jordan JM (2017) Genetic Determinants of Radiographic Knee Osteoarthritis in
44 African Americans. *J Rheumatol* 44:1652-1658
- 45 141. den Hollander W, Boer CG, Hart DJ, Yau MS, Ramos YFM, Metrustry S, Broer L, Deelen J,
46 Cupples LA, Rivadeneira F, Kloppenburg M, Peters M, Spector TD, Hofman A, Slagboom PE,
47 Nelissen R, Uitterlinden AG, Felson DT, Valdes AM, Meulenbelt I, van Meurs JJB (2017)
48 Genome-wide association and functional studies identify a role for matrix Gla protein in
49 osteoarthritis of the hand. *Ann Rheum Dis* 76:2046-2053

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58
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60
61
62
63
64
65
142. Casalone E, Tachmazidou I, Zengini E, Hatzikotoulas K, Hackinger S, Suveges D, Steinberg J, Rayner NW, arc OC, Wilkinson JM, Panoutsopoulou K, Zeggini E (2018) A novel variant in GLIS3 is associated with osteoarthritis. *Ann Rheum Dis* 77:620-623
 143. Baird DA, Paternoster L, Gregory JS, Faber BG, Saunders FR, Giuraniuc CV, Barr RJ, Lawlor DA, Aspden RM, Tobias JH (2018) Investigation of the Relationship Between Susceptibility Loci for Hip Osteoarthritis and Dual X-Ray Absorptiometry-Derived Hip Shape in a Population-Based Cohort of Perimenopausal Women. *Arthritis Rheumatol* 70:1984-1993
 144. Everman DB, Bartels CF, Yang Y, Yanamandra N, Goodman FR, Mendoza-Londono JR, Savarirayan R, White SM, Graham JM, Jr., Gale RP, Svarch E, Newman WG, Kleckers AR, Francomano CA, Govindaiah V, Singh L, Morrison S, Thomas JT, Warman ML (2002) The mutational spectrum of brachydactyly type C. *Am J Med Genet* 112:291-296
 145. Valdes AM, Evangelou E, Kerkhof HJ, Tamm A, Doherty SA, Kisand K, Tamm A, Kerna I, Uitterlinden A, Hofman A, Rivadeneira F, Cooper C, Dennison EM, Zhang W, Muir KR, Ioannidis JP, Wheeler M, Maciewicz RA, van Meurs JB, Arden NK, Spector TD, Doherty M (2011) The GDF5 rs143383 polymorphism is associated with osteoarthritis of the knee with genome-wide statistical significance. *Ann Rheum Dis* 70:873-875
 146. Chen H, Capellini TD, Schoor M, Mortlock DP, Reddi AH, Kingsley DM (2016) Heads, Shoulders, Elbows, Knees, and Toes: Modular Gdf5 Enhancers Control Different Joints in the Vertebrate Skeleton. *PLoS Genet* 12:e1006454
 147. Capellini TD, Chen H, Cao J, Doxey AC, Kiapour AM, Schoor M, Kingsley DM (2017) Ancient selection for derived alleles at a GDF5 enhancer influencing human growth and osteoarthritis risk. *Nat Genet*
 148. Richard D, Liu Z, Cao J, Kiapour AM, Willen J, Yarlagadda S, Jagoda E, Kolachalama VB, Sieker JT, Chang GH, Muthurulan P, Young M, Masson A, Konrad J, Hosseinzadeh S, Maridas DE, Rosen V, Krawetz R, Roach N, Capellini TD (2020) Evolutionary Selection and Constraint on Human Knee Chondrocyte Regulation Impacts Osteoarthritis Risk. *Cell*
 149. Corbani S, Chouery E, Eid B, Jalkh N, Ghoch JA, Megarbane A (2011) Mild Campomelic Dysplasia: Report on a Case and Review. *Mol Syndromol* 1:163-168
 150. Lefebvre V, Dvir-Ginzberg M (2017) SOX9 and the many facets of its regulation in the chondrocyte lineage. *Connect Tissue Res* 58:2-14
 151. Komori T (2019) Regulation of Proliferation, Differentiation and Functions of Osteoblasts by Runx2. *Int J Mol Sci* 20
 152. Klopocki E, Hennig BP, Dathe K, Koll R, de Ravel T, Baten E, Blom E, Gillerot Y, Weigel JF, Kruger G, Hiort O, Seemann P, Mundlos S (2010) Deletion and point mutations of PTHLH cause brachydactyly type E. *Am J Hum Genet* 86:434-439
 153. Feldman GJ, Parvizi J, Levenstien M, Scott K, Erickson JA, Fortina P, Devoto M, Peters CL (2013) Developmental dysplasia of the hip: linkage mapping and whole exome sequencing identify a shared variant in CX3CR1 in all affected members of a large multigeneration family. *J Bone Miner Res* 28:2540-2549
 154. Basit S, Albalawi AM, Alharby E, Khoshhal KI (2017) Exome sequencing identified rare variants in genes HSPG2 and ATP2B4 in a family segregating developmental dysplasia of the hip. *BMC Med Genet* 18:34
 155. Dai J, Shi D, Zhu P, Qin J, Ni H, Xu Y, Yao C, Zhu L, Zhu H, Zhao B, Wei J, Liu B, Ikegawa S, Jiang Q, Ding Y (2008) Association of a single nucleotide polymorphism in growth differentiate factor 5 with congenital dysplasia of the hip: a case-control study. *Arthritis Res Ther* 10:R126
 156. Wang K, Shi D, Zhu P, Dai J, Zhu L, Zhu H, Lv Y, Zhao B, Jiang Q (2010) Association of a single nucleotide polymorphism in Tbx4 with developmental dysplasia of the hip: a case-control study. *Osteoarthritis Cartilage* 18:1592-1595
 157. Shi D, Dai J, Zhu P, Qin J, Zhu L, Zhu H, Zhao B, Qiu X, Xu Z, Chen D, Yi L, Ikegawa S, Jiang Q (2011) Association of the D repeat polymorphism in the ASPN gene with developmental dysplasia of the hip: a case-control study in Han Chinese. *Arthritis Res Ther* 13:R27

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54
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58
59
60
61
62
63
64
65
158. Cengic T, Trkulja V, Pavelic SK, Ratkaj I, Markova-Car E, Mikolaucic M, Kolundzic R (2015) Association of TGFB1 29C/T and IL6 -572G/C polymorphisms with developmental hip dysplasia: a case-control study in adults with severe osteoarthritis. *Int Orthop* 39:793-798
159. Jia J, Li L, Zhao Q, Zhang L, Ru J, Liu X, Li Q, Shi L (2012) Association of a single nucleotide polymorphism in pregnancy-associated plasma protein-A2 with developmental dysplasia of the hip: a case-control study. *Osteoarthritis Cartilage* 20:60-63
160. Hao Z, Dai J, Shi D, Xu Z, Chen D, Zhao B, Teng H, Jiang Q (2014) Association of a single nucleotide polymorphism in HOXB9 with developmental dysplasia of the hip: a case-control study. *J Orthop Res* 32:179-182
161. Tian W, Zhao L, Wang J, Suo P, Wang J, Cheng L, Cheng Z, Jia J, Kan S, Wang B, Ma X (2012) Association analysis between HOXD9 genes and the development of developmental dysplasia of the hip in Chinese female Han population. *BMC Musculoskelet Disord* 13:59
162. Liu S, Tian W, Wang J, Cheng L, Jia J, Ma X (2014) Two single-nucleotide polymorphisms in the DKK1 gene are associated with developmental dysplasia of the hip in the Chinese Han female population. *Genet Test Mol Biomarkers* 18:557-561
163. Zhao L, Tian W, Pan H, Zhu X, Wang J, Cheng Z, Cheng L, Ma X, Wang B (2013) Variations of the COL1A1 gene promoter and the relation to developmental dysplasia of the hip. *Genet Test Mol Biomarkers* 17:840-843
164. Sun Y, Wang C, Hao Z, Dai J, Chen D, Xu Z, Shi D, Mao P, Teng H, Gao X, Hu Z, Shen H, Jiang Q (2015) A common variant of ubiquinol-cytochrome c reductase complex is associated with DDH. *PLoS one* 10:e0120212
165. Salazar VS, Gamer LW, Rosen V (2016) BMP signalling in skeletal development, disease and repair. *Nat Rev Endocrinol* 12:203-221





Noggin, Chordin, Gdf, Bmp, Wnt
 Gdf, Patched Gdf, Wnt
 Bmp Ihh Noggin Pthrp

