Clin Orthop Relat Res (2012) 470:3284–3296
DOI 10.1007/s11999-012-2511-4

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

SYMPOSIUM: ABJS CARL T. BRIGHTON WORKSHOP ON HIP PRESERVATION SURGERY

Hip Ontogenesis: How Evolution, Genes, and Load History Shape Hip Morphotype and Cartilotype

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Published online: 28 August 2012
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Abstract

Background Developmental hip disorders (DHDs), eg, developmental dysplasia of the hip, slipped capitis femoris epiphysis, and femoroacetabular impingement, can be considered morphology variants of the normal hip. The femoroacetabular morphology of DHD is believed to induce osteoarthritis (OA) through local cumulative mechanical overload acting on genetically controlled patterning systems and subsequent damage of joint structures. However, it is unclear why hip morphology differs between individuals with seemingly comparable load histories and why certain hips with DHD progress to symptomatic OA whereas others do not.

Questions/Purposes We asked (1) which mechanical factors influence growth and development of the proximal femur; and (2) which genes or genetic mechanisms are associated with hip ontogenesis.

Methods We performed a systematic literature review of mechanical and genetic factors of hip ontogeny. We focused on three fields that in recent years have advanced our knowledge of adult hip morphology: imaging, evolution, and genetics.

Where Are We Now? Mechanical factors can be understood in view of human evolutionary peculiarities and may summate to load histories conducive to DHD. Genetic factors most likely act through multiple genes, each with modest effect sizes. Single genes that explain a DHD are therefore unlikely to be found. Apparently, the interplay between genes and load history not only determines hip morphotype, but also joint cartilage robustness ("cartilotype") and resistance to symptomatic OA.

Where Do We Need to Go? We need therapies that can improve both morphotype and cartilotype.

How Do We Get There? Better phenotyping, improving classification systems of hip morphology, and comparative population studies can be done with existing methods. Quantifying load histories likely requires new tools, but proof of principle of modifying morphotype in treatment of DDH and of cartilotype with exercise is available.

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All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research* editors and board members are on file with the publication and can be viewed on request.

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Introduction

Hip ontogenesis, or morphogenesis, describes the development of the hip from its fetal origin to the adult form. Developmental hip disorders (DHDs) such as developmental dysplasia of the hip (DDH), slipped capitis femoris epiphysis (SCFE), or femoroacetabular impingement (FAI) may cause symptoms and disability in adulthood or earlier as a result of altered joint morphology [24, 49, 85, 106]. Regardless of being primarily acetabular or femoral, DHDs share a common mechanism of local cumulative

mechanical overload and damage of joint structures that may cause osteoarthritis (OA) [24, 31]. Interventions that decrease DHD incidence may thus decrease OA disease burden. However, such interventions should be based on good explanations of hip ontogeny and OA development. Current explanations for skeletogenesis and bone morphology imply an important role of mechanical loading, explicitly [15, 35], or more implicitly [79], acting on genetically controlled patterning systems [25, 54, 110]. Although detailed explanations are available from animal models [25, 68, 79], this knowledge is as yet not very useful to decrease DHD prevalence nor applicable for individual patients. For example, it is currently unclear why important hip morphology differences exist between individuals or populations with comparable load histories [37, 112] (nor why these differences appear larger for hips than knees). Clearly, genetic differences may account for these morphological differences. However, genes have only recently been linked to hip morphology [5, 53, 103] and genetic architecture for hip morphogenesis is apparently complex and polygenic with modest effect size for individual genes (ie, no genes specific for each DHD have been found). Furthermore, it is currently unclear why certain hips with DHD progress to symptomatic OA, whereas others do not [6, 106]. We propose integrating observations from several fields that have recently advanced understanding of adult hip morphology (ie, imaging, evolution, and genetics) can improve our explanations of hip ontogeny and OA development.

Imaging studies using new parameters and image analysis allow comprehensive quantification of proximal femoral morphology [27, 65, 99] and have strengthened the association between morphology and OA development or prevalence [19, 28, 29, 55, 64].

Observations from evolution studies comparing humans with other large apes indicate the growing human lower limbs with open physes and long moment arms can undergo high loading for several years (eg, in sports). When compared with other animals (eg, mice and chickens), experimental models have begun to elucidate the fundamental molecular, mechanical, and genetic mechanisms and their interactions in skeletogenesis.

Genetic studies, in the last decade, have begun to explore the relation between loading and gene expression [7, 67, 79] and, more recently, between genes and hip morphology [5, 103]. These studies indicate that the same genes active in skeletogenesis, for example through regulation of growth plate chondrocytes, may also play a role in OA development in later life.

We therefore performed a systematic literature review of (1) mechanical factors that influence growth and development of the proximal femur in animals and humans; and (2) genes or genetic mechanisms associated with hip ontogenesis. We specifically sought to identify information on the (potential) interaction between mechanical and genetic factors. Furthermore, we sought information from the three fields described previously that, in recent years, have advanced our knowledge of adult hip morphology: imaging, evolution, and genetics. Because OA development is related to morphology variants, we discussed our findings with respect to DHD.

Methods: Search Strategy and Criteria

We performed three searches in Medline, Embase, and Web of Science summarizing the literature on mechanical and genetic factors of hip growth and development. For these searches we formed six groups of search terms and one group with exclusion terms composed by the first three authors in joint discussion. The first group, Group A, referred to terms related to "the hip", Group B to "growth and development", Group C to "mechanical factors", Group D to "genetic factors", Group E to "DHD", and Group F referred to "prevalence". Group G consisted of exclusion terms and was composed of irrelevant title words found during pilot searches (see Appendix).

For each search we combined three groups of terms. For example, to investigate the influence of mechanical factors on hip growth and development, we combined Groups A, B, and C. They were connected using the Boolean operator AND. In addition, Group G was added using the Boolean operator NOT. Terms within a group were combined using the Boolean operator OR. All search terms and group combinations are reported in the Appendix. The search field was "title and abstract" combined with MESH terms when using Medline. The search field for exclusion terms was "title" only. The three searches resulted in three lists of articles for each database. These lists were then searched based on titles and abstracts and had to contain specific reference to mechanical or genetic aspects of hip ontogeny, or imaging and image analysis, or evolution, embryology, or genes. Articles that did not contain any of these subjects were excluded. Also, articles written in languages other than English, German, French, or Dutch were excluded. After selection, further articles were added from reference lists of included articles.

The first search, regarding the effect of mechanical phenomena on growth and development of the proximal femur in both humans and animals, yielded more than 13,500 results. The second search for genes and genetic mechanisms associated with skeletogenesis and the hip resulted in more than 8500 articles. The third search was focused on prevalence of DDH, SCFE, and FAI with regard to different populations, twin studies, and sex. More than 3500 articles were found.

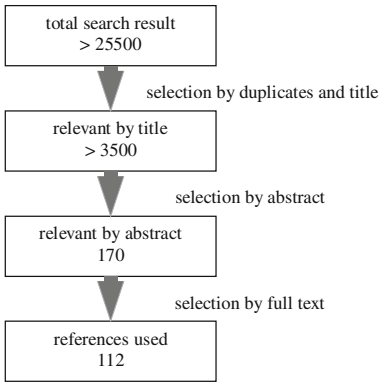

Fig. 1 Flowchart for evaluation of literature.

Of the more than 25,500 publications found in total, 25,330 were irrelevant based on duplicates, title, and abstract, leaving 170 publications for evaluation (Fig. 1).

Results

Imaging and Quantification of Hip Morphology

Parameters for measuring hip morphology currently relate to concavity, a compound measure determined by femoral head sphericity, relative neck width, and offset (femoral head position relative to the neck) [99]. Previously hip morphology was mostly described without quantifying the sphericity of the femoral head or its relationship to the femoral neck. Goodman et al. [26] introduced the concept of concavity of the femoral head-neck junction in 1997 followed by its quantification with the alpha angle in 2002 [65]. Similar angles characterize concavity in other planes [8, 22, 38, 99]. Concavity is a measure of the potential ROM of the proximal femur in the acetabulum before bony contact occurs and mostly used to describe the cam morphotype of FAI. Acetabular measurements of version and center-edge angle [107] currently quantify the pincer morphotype of FAI [24]. Clearly, imaging for the next decade needs to integrate femoral and acetabular parameters to further our understanding of hip morphology and function.

Methods for image analysis of hip morphology now include statistical shape models (SSMs) [29]. SSMs can be used to compare complex three-dimensional morphology without the need to assume ideal geometry, eg, a spherical femoral head. An SSM of the hip can be built by placing a large number of points (eg, 70) on AP pelvis radiographs on designated locations of the femur, acetabulum, and pelvis [103]. Statistical methods then construct an average hip shape from all radiographic points in all patients, and a computer algorithm (principle component analysis) recombines these into "shape modes," which constitute the SSM. Each shape mode describes a distinct change in hip morphology, a number of SDs away from the cohort's average shape. SSMs are used increasingly to describe complex morphology [29, 55, 88], but as yet there are no studies that show how shape modes correlate to FAI morphotypes (cam and pincer).

We found no quantitative imaging studies for any mammal, including humans, of femoral head and head-neck morphology development from embryo to adult. Nevertheless, qualitative comparison of intrauterine and perinatal hip morphology with adult hip morphology shows the relatively unloaded intrauterine femoral head is round in fairly uniform degree but that morphology develops during postnatal locomotor development into more or less spherical femoral heads. Examples can be found for the rabbit [108], cow [90], and primates [2, 4]. Postnatal diversion of hip morphology in itself does not imply it is attributable only to the loading of locomotor development; it can also be the expression of genetic pattern formation [54, 110]. These issues can be further explored in animal models in which the limb muscles are absent or paralyzed in utero.

Mechanical Factors and Embryology

Mechanical factors in early hip morphogenesis can be studied by blocking muscle contraction in experimental embryo models. The mouse embryo is the best studied animal model for mammalian development [68] with many genetic manipulations and molecular tools available, eg, genetically modified mice with altered, reduced, or absent muscles. Another model is the chick embryo paralyzed with a neuromuscular blocking agent [79]. Although long bone development is endochondral in mice, and intramembranous in chicks, reduced or absent mechanical loading affects bone and joint formation in both. Absence of muscle contractions does not alter the first phase in joint development (interzone formation [21]). However, the next phase, joint space development (cavitation), is characterized by changes in gene expression and histology of the developing joint tissues. Gene activation in response to loading has recently been documented in both animal models [7, 41, 42, 67]. In muscle-paralyzed chicks, all bones and synovial joints are affected in the absence of muscle contraction, but in mice, some early bone and joint structures are unaffected [68]. This difference is likely the result of the uterus wall that generates mechanical forces affecting the embryo as opposed to the rigid nongrowing eggshell of birds [68]. Thus, local mechanical stimuli appear to provide positional information, guiding genetic patterning and morphogenesis. Further clues indicate static loading is needed for bone modeling, whereas motion would be mainly involved in joint development [70].

Mechanical Factors and Evolution

Mechanical factors in human hip ontogeny can also be studied by comparing with quadrupedal mammals and the other large apes. The human fetus has a very large head, long legs, and is positioned in an upright mother. In quadrupedal mammals, the abdomen and uterus hang under a horizontal spine like a hammock. Early 20th century authors [13, 48] proposed the uterus wall hyperflexes the human hip, levering the long femur against the prominent anterosuperior iliac spine. This levering is assumed to lower femoral head pressure in the acetabulum, decreasing its relative depth, and to create a torsional moment on the femur increasing anteversion [48]. The large apes, having smaller heads, shorter legs, and a flat ilium without prominent iliac spines, are indeed without hip dysplasia (except one single gorilla [91]). Thus, mechanical factors may adequately explain human neonatal/infant hip dysplasia. Several studies have corroborated these earlier pathomechanical concepts [13, 18], for increasing femoral version [11, 40, 73, 105] and decreasing relative acetabular depth [73, 104]. Furthermore, anteversion increases in rabbits splinted in flexion-external rotation; flexion-internal rotation produces retroversion [108]. Likewise, postnatal femoral detorsion is a consistent finding in normal hip development [69].

Humans walk with approximately 5° hip extension at toe-off while prone extension is approximately 10° to 20° [77, 78]. Active hip flexion is 120°, whereas walking flexion is approximately 35° and running 50° [66]. Thus, the human weightbearing range of hip motion shifts close to its extension limit during bipedal gait development. Quadrupeds bear weight closer to midrange hip flexion [3], and femoral neck anteversion then acts to align the capital growth plate more perpendicular to the vertical gait forces [96]. The human extended hip position diminishes this mechanical advantage anteversion can have on shear forces on the capital physis. Furthermore, the human capital physis, nearly horizontal in neonates, tilts to approximately 30° more vertical in adolescence. Both mechanisms render the capital physis more vulnerable to shear forces.

The large apes walk bipedally but do not run bipedally [20]. Moreover, human growth and development is 5 to 6 years longer compared with chimpanzees, which reach adulthood at 11 to 12 years [84, 95]. Human lower limbs have much longer moment arms than the large apes [82]. Corrected for body weight, peak hip forces in humans are much higher than quadrupeds, increasing further with running or sports [9, 10]. These factors can summate to a load history of enduring high loads on the growing hip.

Thus, species-specific mechanical factors in human hip ontogeny can be interpreted to explain neonatal/infant hip dysplasia, to increase shear forces on the capital physis that may induce SCFE, and to create a load history that may induce morphologic changes in the growing hip.

Genetic Factors, Human Hip Morphogenesis, and Osteoarthritis Development

Genetic factors orchestrate hip morphogenesis. Nonetheless, specific underlying genes have thus far not been identified for the three common DHDs [53]. Genetic architecture for hip morphogenesis is most likely complex and polygenic with modest effect size for individual genes [53], similar perhaps to genetic factors for height [46]. Further indications of the polygenic nature of hip morphogenesis are associations of DDH to other skeletal abnormalities, eg, facial, whether part of an established syndrome [47] or not [32].

Morphology variants such as DDH and FAI are known morphological risk factors for onset of hip OA [45, 94]. Therefore, many researchers used a genetic approach to elucidate underlying OA mechanisms, but only recently have such studies begun to incorporate hip morphology analysis. Genetic methods include genomewide association studies (GWASs), testing many common genetic variants in different individuals for their association with OA [101]) and candidate gene studies that test specific genes, ie, those involved in skeletogenesis (Table 1).

Indeed, the majority of best-confirmed OA susceptibility genes appear involved in skeletal morphogenesis and/or cartilage and bone homeostasis (Table 1) [5, 16, 52, 56, 57, 76, 81, 86, 100, 102, 103]. This raises the question whether genetic variants cause subtle skeletal malformations that increase mechanical stress on articular cartilage surfaces, initiating OA [12].

Pollard and coworkers [71] found that siblings of patients with FAI have a higher prevalence of cam morphotype than control subjects (relative risk 2.8). Moreover, siblings had more clinical signs of FAI (eg, positive impingement test) than control subjects with the same FAI morphology (relative risk 2.5). This suggests an additional genetic component, beyond the increased risk of abnormal morphology, may be involved in the development of OA [71].

Using a statistical shape model to analyze hip morphology in sibling pairs, Waarsing and coworkers [103] found high heritability estimates for four hip shape modes, ie, hip morphology was under strong genetic influence. Exploring the association between OA susceptibility genes and hip morphology further, they found carrier status of one OA susceptibility variant in the deiodinase-iodothyronine, type 2 gene was associated with OA but more likely through increasing the cartilage vulnerability to mechanical stress by nonoptimal hip morphology [103].

Table 1. Human genetic studies for association with hip and knee osteoarthritis

Gene	Study design, population	Protein	Function	Mechanism	Study outcome	Comment
ASPN [81, 86]	Asians	Asporin	Extracellular matrix macromolecule from proteoglycan protein family	Asporin may inhibit TGFß	ASPN is associated with DDH in Chinese	Effects shown in Asian populations
DIO2 [56, 103]	Genomewide linkage Europeans Hip OA	Deiodinase 2 (D2)	DIO2 encodes enzyme D2	D2 regulates availability of active thyroid hormone T3, important for long bone formation	DIO2 relates to both morphotype and cartilotype of the hip	First to relate gene to form to OA; SSM not related to cam/pincer?
GDF5 [57, 100]	Candidate gene Asian European	GDF5 (from TGFß superfamily and related to BMP)	GDF5 is regulator of cell growth and differentiation in both embryonic and adult tissues	GDF5 is involved in bone and joint formation and also expressed in soft tissue joint structures	Decreased GDF5 expression may lead to increased OA susceptibility [57, 76] GDF5 is associated with 17% risk increase of knee OA (OR, 1.17; 95% CI, 1.12–1.23)	GDF5 insufficient mice develop OA [16]
FRZB [5]	White women ≥ 65 years	sFRP3	Encodes sFRP3, and inhibits WNT signaling in both embryos and adults	WNT signaling in chondrocytes and osteoblasts is important in cartilage and bone homeostasis and during skeletal patterning in embryogenesis	FRZB influences both morphotype and cartilotype of the hip	FRZB knockout mice develop OA [52] Shape Mode 2 relates to lack of head-neck offset? [5]
SMAD3 [102]	European	SMAD3 protein, member of TGFß superfamily	Smad3 is a key intracellular messenger in TGF signaling pathway	TGFß/Smad3 signaling has been shown to be essential for maintaining articular cartilage	Genetic variation in the SMAD3 gene has a role in the risk of large-joint OA OA hip OR, 1.22 OA knee OR, 1.12	

OA = osteoarthritis; TGF = tumor growth factor; BMP = bone morphogenic protein; DDH = developmental dysplasia of the hip; OR = odds ratio.

A similar study found variant alleles of the FRZB genes influence both hip morphology and the relationship between hip morphology and OA [5]. Thus, all three studies that examined the relation between hip morphology, genes and OA, find it is not morphology alone that is associated with OA, but likely a combination with a genetically determined cartilage vulnerability.

In analogy to morphotype, this cartilage vulnerability or robustness (including subchondral bone) can be conceptualized as cartilotype, ie, the ability of cartilage to withstand mechanical stress. Thus, a hip can have unfavorable morphotype, but favorable cartilotype, and may not develop progressive OA. Conversely, it may have only minor suboptimal morphology, but unfavorable cartilotype, and develop OA. For both scenarios, OA development will be influenced by load history determined by frequency and magnitude of all loads (Fig. 2). This concept may explain prospective studies with 10 to 40 years followup that show a substantial proportion of subjects with an FAI or DDH morphotype does not develop progressive OA [6, 34, 106].

Developmental Dysplasia of the Hip

Compared with life after birth, the hip experiences a more uniform load history in utero. Prevalence differences in healthy single-birth primiparous neonate DDH therefore suggest genetic differences explain the occurrence of DDH rather than in utero positioning. (This may not apply to twin pregnancies in which clear differences in load history may exist when one fetus has its knees extended and the other flexed.)

Indeed, neonate DDH varies widely between ethnic groups, from 0.87 per 1000 live births in Hong Kong Chinese [98] to 10.5 per 1000 in southern Australia [111]. A recent twin study [17] confirms a notion proposed earlier [109] that flexed knees in utero decrease DDH prevalence. Taken together, these findings indicate a strong genetic factor in DDH. Correspondingly, large population studies show a 12-fold increase in risk for first-degree relatives and siblings [92]. Prevalence of neonatal and infant DDH has been reduced considerably by education, screening, and early treatment programs [61].

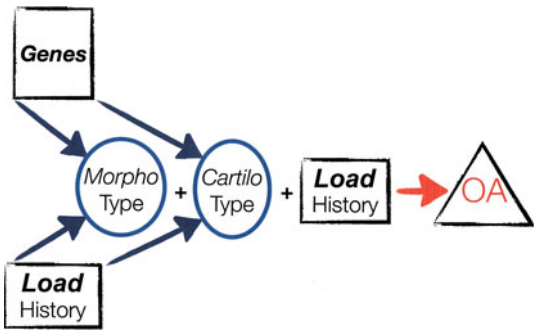

Fig. 2 Interplay of genes, load history produces morphotype, interplay of morphotype, cartilotype (see text), and load history may or may not lead to OA.

Slipped Capital Femoris Epiphysis

Incidence of SCFE varies widely between ethnic groups, ie, approximately 4.5 per 100,000 in Polynesian children and 0.1 (girls) to 0.5 (boys) in Korean children [50]. Further genetic influences have been shown in several ethnic groups and within families [50, 51, 63]. Increasing prevalence has been documented repeatedly over the last 20 years in each study related to increasing obesity [58, 63, 89].

The cam, pistol grip, or head tilt morphotype has been interpreted as a subclinical slip of the femoral epiphysis [26, 33, 59], but none of these authors examined the age cohort in which this slip supposedly occurs. Recently, two studies (discussed subsequently) reported cam morphotype prevalence in a total of 256 men aged 9 to 25 years [87] and 12 to 19 years [1] but found no clinical, MRI [87], or radiographic [1] signs of SCFE. Furthermore, Siebenrock and coworkers [87] showed earlier that the direction of tilt of the capital epiphysis in SCFE, posteroinferior, differs from the anterosuperior extension of the physis in cam morphotype.

Femoroacetabular Impingement

FAI morphotypes are unknown as yet in childhood (before the age of 10 years) [69]. This is unknown as yet, because this may also be related to the present lack of hip morphology studies of large populations of children using multiple plane or three-dimensional imaging techniques. We found no longitudinal studies demonstrating development of FAI morphotypes. Neither are there longitudinal studies demonstrating the effect of loading on hip morphology in children or adolescents. However, two cross-sectional studies in adolescents indeed suggest such a relation.

In 1971, Murray and Duncan [60] proposed a relation between athletic activity and hip morphology. However, the characteristics of study and control groups were not adequately defined to allow clear statements about the effect of load history on the hip. What the study did show, however, was high prevalence of cam morphotype ("tilt deformity") in an adolescent English population, particularly considering that only AP radiographs were used, making underestimation of cam prevalence likely [22].

Forty years later, Siebenrock and coworkers used radial MRI scans to compare cam prevalence in 37 competitive basketball players, aged 9 to 25 years, with 38 weight- and age-matched nonsports control subjects. They found higher alpha angles in the athletes than control subjects (average 60.5° ± 9° and 47.4° ± 4°, respectively). Intriguingly, these differences were more pronounced in players with a closed capital physis, indicating an ongoing effect of load history after physeal closure.

Agricola et al. [1] compared hip morphology in 89 preprofessional soccer players, aged 12 to 19 years, with 92 age-matched control subjects. In this study, sports activity was not systematically documented in the control subjects, and 84% of control subjects were seen initially for hip complaints, although none revisited this hospital during the next 2 years. Cam morphotype prevalence was increased in the soccer players when assessed by shape of the femoral head-neck junction (ie, normal, flat, bump), but not when only radiographic alpha angles > 60° were compared (26 % versus 17% for soccer players and control subjects, respectively).

Thus, high-intensity sports during adolescence may be associated with a higher prevalence of cam morphotype. However, these are findings in white European populations. In other populations, for example Asian populations, cam morphotype prevalence appears to be very low (Table 2) [28, 30, 43, 44, 59, 62, 65, 72, 75, 93, 99]. Accordingly, studies comparing Asian and white populations with identical methods found rounder femoral heads, ie, higher proximal femoral concavity in Asians [23, 36]. Therefore, it appears unlikely it is only sports participation that causes cam morphotype. More likely, genetic factors also influence susceptibility to a given load history.

Discussion

In a systematic literature review we examined three fields that may add information to the explanation of hip ontogeny and OA development: imaging, evolution, and genetics. Incorporating advances in these fields in existing mechanical and genetic explanations may further our understanding of hip ontogeny and OA development. Because OA development is related to morphology variants of DHD, we discussed our findings with respect to DDH, SCFE, and FAI.

Where Are We Now?

During the course of our literature review, we identified a number of limitations in approaches and the literature that precludes a better understanding of the relationship of load history and genetics in hip development. First, as a result of the human evolutionary peculiarities, we currently lack an appropriate animal model that mimics human hip ontogeny. Second, to study load histories in hip morphogenesis, we likely need new and precise tools to quantify these loads. Furthermore, evidence shows tissues ignore the large majority of a loading experience, but our understanding about which part of a load history primarily triggers morphological change is limited [14]. Third, experimental data, particularly genetic, are expanding rapidly, but translation to therapeutic studies in humans awaits better phenotyping of patients.

An unresolved issue, but an important one to guide future clinical studies, is whether hip morphology is primarily determined by genetic or mechanical factors. Genetic factors, although evident in DDH, SCFE, and FAI, most likely act through several or numerous genes, each with modest effect sizes. In other words, single genes that explain a DHD have not been identified nor is it likely they will be [53]. Mechanical factors can be understood in view of human evolutionary peculiarities. Starting in utero, and continuing with development of upright gait and slow skeletal maturation, they may summate to load histories conducive to DHD. Conversely, an emerging body of evidence documents an interplay between genetic and mechanical factors in the development of hip morphotype.

Whether a given hip morphotype will lead to progressive OA is, again, influenced by mechanical factors, ie, load history, but appears influenced also by the ability of cartilage to withstand mechanical stress, ie, “cartilotype” (Fig. 2).

Where Do We Need to Go?

We need therapies that can improve both morphotype and cartilotype. In guiding future studies, we can distinguish what can be done using currently available tools and those that likely require development of new tools or technology.

How Do We Get There?

Studies That Can Be Done Using Current Tools

Further identification of genes involved in the complex interactions of morphogenesis and development of OA, ie, morphotype and cartilotype, can be done with existing tools but requires a multidisciplinary approach with GWASs in thousands of cases and control subjects.

Table 2. Prevalence of cam deformity in white male control subjects and Asian control subjects and Asian patients undergoing THA: cam morphotype prevalence varies with ethnicity, age, and imaging parameters

Study	Population	Age	Imaging	Parameter measured	Percent cam morphotype
Murray, 1965 [59]	25 English male control subjects	–	AP pelvic radiographs	"Head tilt deformity" femoral head ratio (FHR) > 1.35	10%
Nötzli et al., 2002 [65]	17 Swiss male control subjects with ≥ 20° internal rotation in 90° flexion	30 ± 5 years	MRI	Alpha angle > 50° at 3:00 position	0%
Gosvig et al., 2010 [28]	1332 Danish male control subjects population study	60 ± 13.6 years	AP pelvic radiographs	"Pistol grip deformity" triangular index	19.6%
Reichenbach et al., 2010 [75]	244 Swiss male control subjects 18-year-old army recruits	19.9 years	Radial MRI	Decreased offset head-neck junction anterior quadrant (0–3:00)	24%
Hack et al., 2010 [30]	90 Canadian male control subjects (79% whites)	29.4 years	Radial MRI	Alpha angle > 55° at 1:30 position	51.6%
Pollard et al., 2010 [72]	39 English male control subjects without hip signs or symptoms	47.5 ± 12 years	Crosstable lateral radiographs	Alpha angle > 62°	2.6%
Laborie et al., 2011 [44]	874 Norwegian male control subjects population study	18.6 ± 0.6 years	AP pelvic radiographs	Pistol-grip deformity focal femoral neck prominence flattening of lateral femoral head	21.5% pistol-grip deformity; 10.3% focal neck prominence; 14.4% flattening of femoral head
Toogood ≤ 50 years [99]	140 US (Cleveland) cadaver femora; 50% whites and 50% blacks	37 years	Photographs	Alpha angle > 55° at 3:00 position	18.6%
Toogood et al., 2009 (> 50 years) [99]	48 US (Cleveland) cadaver femora; 50% whites and 50% blacks	63 years	Photographs	Alpha angle > 55° at 3:00 position	43.8%
Kim, 1989 [43]	172 Korean fetuses; 67 male adult cadavers; 244 male Korean adults hospitalized for other reasons than hip	14–38 weeks 60.6 years 58.4 years	Caliper measurement/ 244 AP pelvic radiographs	Femoral head sphericity (caliper); femoral head sphericity (caliper); femoral head sphericity (Mose ring on radiograph)	"Spherical femoral heads in fetal and adult cadavers"; spherical femoral heads on radiographs, "no pistol grip"
Takeyama et al., 2009 [93]	158 Japanese male patients undergoing THA	–	Preoperative crosstable lateral radiographs	Alpha angle > 60°	1.6%
Nakahara et al., 2011 [62]	21 Japanese male control subjects (36 hips)	72.7 ± 5.7 years	Three-dimensional CT	Alpha angle > 55° at 1:00 position	25%

GWASs can only identify variation in DNA that is relatively common in a population. Newer tools such as exome sequencing can help find causative genes for hip morphotypes. Exome sequencing narrows down the search because it examines only the (1.5%) portion of the genome that is expressed as protein [97], allowing a much larger

number of samples to be sequenced. A combination of methods will likely yield the most interesting results.

Imaging for the next decade needs to integrate femoral and acetabular parameters, allow motion simulation, and analysis of large patient populations. The first two depend on improved analysis of CT or MRI and the latter on (semi-)automated analysis (eg, SSM). Currently, most prospective data of hip development and morphology are available only in conventional radiographs. Reconstructing the three-dimensional shape of the pelvis and hip from these two-dimensional images would be highly valuable. SSM-based techniques for this have already been described and await clinical use [83].

A combination of these genetic and imaging data can clarify how (defects of) implicated genes cause the actual disease phenotype. This can lead to more prognostic classification systems that may improve and individualize patient care.

Studies That May Need New Technology/Tools

Meaningful quantification of load history requires new tools for both experimental and clinical measurement but also depends on better understanding of which part of a load history triggers morphological change. Ultimately, integrating information on morphotype, cartilotype, and load history may allow us to better predict the future hip function for an individual patient.

Nonetheless, proof of principle of modifying morphotype is already available in the effectiveness of early treatment programs for infant DHD. Similar programs can be envisaged for FAI, but guiding hip morphogenesis may be a very different and more difficult task in adolescents than infants. Screening for FAI may already be done using a ROM testing apparatus [74].

Proof of principle of modification of cartilotype and its assessment has been given for the knee, in which an exercise program led to improved cartilage quality as assessed by delayed gadolinium-enhanced MRI (dGEMRIC quantifies cartilage glycosaminoglycan [GAG] concentrations; T2 [transverse relaxation time] mapping evaluates cartilage hydration and collagen fiber integrity [39]). This study only examined the effect of exercise on cartilage quality [80], but biochemical or genetic modification of cartilotype may also become therapeutic options.

Appendix: search strategy and criteria

We performed three searches in Medline, Embase, and Web of Science summarizing the literature on mechanical and genetic factors of hip growth and development. For these searches we formed six groups of search terms and one group with exclusion terms composed of the first three authors in joint discussion. The first group, Group A, referred to terms related to "the hip", Group B to "growth and development", Group C to "mechanical factors", Group D to "genetic factors", Group E to "DHD", and Group F referred to "prevalence". Group G consisted of exclusion terms and was composed of selecting irrelevant title words found during pilot searches.

For each search we combined three groups of terms. For example, to investigate the influence of mechanical factors on hip growth and development, we combined Group A, B, and C. They were connected using the Boolean operator AND. In addition, Group G was added using the Boolean operator NOT. Terms within a group were combined with the Boolean operator OR. All used search terms and group combinations are reported in the Appendix. The search field was "title and abstract" combined with MESH terms when using Medline. The search field for exclusion terms was "title" only. The three searches resulted in three lists of articles for each database. These lists were then searched based on titles and abstracts and had to contain specific reference to mechanical or genetic aspects of hip ontogeny, or imaging and image analysis, or evolution, embryology, or genes. Articles that did not contain any of these subjects were excluded. Also, articles written in other languages than English, German, French, or Dutch were excluded. After selection, further articles were added from reference lists of included articles.

The first search, regarding the effect of mechanical phenomena on growth and development of the proximal femur in both humans and animals, yielded over 13,500 results. The second search for genes and genetic mechanisms associated with skeletogenesis and the hip resulted in more than 8500 articles. The third search was focused on the prevalence of DDH, SCFE, and FAI with regard to different populations, twin studies, and sex. Over 3500 articles were found.

Of the more than 25,500 publications found in total, 25,330 were irrelevant based on duplicates, title, and abstract, leaving 170 publications for evaluation (Fig. 2).

A Terms related to the hip	B Terms related to growth and development	C Terms related to mechanical factors	D Terms related to genetic factors	E Terms related to DDH, SCFE, FAI	F Terms related to prevalence	G Exclusion terms
hip	development	biomechanics	genetic	impingement	ethnic	cerebral palsy
femur	growth	stress	genes	FAI	prevalence	prostheses
head	ontogeny	sports	gene	dislocation	incidence	osteotomy
femoral	fetus	sporting	aetiology	hip	gender	fracture
head	fetal	athletic	etiology	dysplasia	population	fractures
femur	intrauterine	activity	genetics	disease	asian	arthroplasty
neck	intra-uterine	weight-Bearing	polymorphism	hip	asia	replacement
femoral	intra uterine	weight Bearing	twins	slipped	japanese	implant
neck	prenatal	exercise	twin	epiphysiolysis	japan	implants
femoral	pregnancy	movement	family	epiphysiolyses	africa	obesity
torsion	trimester	posture	gdf5	SCFE	european	diabetes
proximal	antenatal	load	frzb	DDH	britain	blood pressure
femur	young	loading	dio2	cam	french	adiposity
proximal	adolescent	gait	calm1	pincer	north american	component
femoral	child	mechanical	smad3	SUFE	north america	components
acetabulum	infant	running	biological evolution	morphology	german	obese
Epiphyses	children	motor		morphometric	germany	metabolic
epiphysis	childhood	activity			Spanish	syndrome
growth	puberty	locomotion			spain	liver
plate	neonatal	pressure			racial	cardiovascular
	neonate	stability			race	
	neonates	shape			caucasians	
	toddler				caucasian	
	toddlers				chinese	
	schoolchildren				china	
	schoolchild				korea	
	infants				korean	
	youth				united kingdom	
	evolution				france	

List of the terms used in the searches categorized in seven groups. Terms within a group were combined using the Boolean operator OR.

To find publications on the effect of mechanical factors on hip growth and development, we combined search terms A AND B AND C NOT G.

To find publications regarding genetic factors associated with hip growth and development, we combined A AND B AND D NOT G.

To find publications on prevalence of DDH, SCFE, and FAI in different populations, we combined search terms A AND E AND F NOT G.

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