Genetic influences in the aetiology of femoroacetabular impingement

A SIBLING STUDY

T. C. B. Pollard,
R. N. Villar,
M. R. Norton,
E. D. Fern,
M. R. Williams,
D. W. Murray,
A. J. Carr

From the University of Oxford, Oxford, England

■ T. C. B. Pollard, BSc(Hons), MRCS, Specialist Registrar, Botnar Surgical Research Fellow
■ D. W. Murray, MD, FRCS(Orth), Professor of Orthopaedic Surgery
■ A. J. Carr, ChM, FRCS, Nuffield Professor of Orthopaedic Surgery
Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences University of Oxford and Nuffield Orthopaedic Centre NHS Trust, Windmill Road, Headington, Oxford OX3 7LD, UK.
■ R. N. Villar, MS, FRCS, Consultant Orthopaedic Surgeon
The Wellington Hospital, South Building, 8a Wellington Place, St John's Wood, London NW8 9LE, UK.
■ M. R. Norton, FRCS(Orth), Consultant Orthopaedic Surgeon
■ E. D. Fern, FRCS(Orth), Consultant Orthopaedic Surgeon
Royal Cornwall Hospitals NHS Trust, Treliske, Truro, Cornwall TR1 3LJ, UK.
■ M. R. Williams, FRCS(Orth), Consultant Orthopaedic Surgeon
Plymouth Hospitals NHS Trust, Derriford Hospital, Derriford Road, Crownhill, Plymouth, Devon PL6 8DH, UK.
Correspondence should be sent to Mr T. C. B. Pollard; e-mail: Tom.Pollard@ndorms.ox.ac.uk

Femoroacetabular impingement causes pain in the hip in young adults and may predispose to the development of osteoarthritis. Genetic factors are important in the aetiology of osteoarthritis of the hip and may have a role in that of femoroacetabular impingement. We compared 96 siblings of 64 patients treated for primary impingement with a spouse control group of 77 individuals. All the subjects were screened clinically and radiologically using a standardised protocol for the presence of cam and pincer deformities and osteoarthritis.

The siblings of those patients with a cam deformity had a relative risk of 2.8 of having the same deformity (66 of 160 siblings hips versus 23 of 154 control hips, p < 0.00001). The siblings of those patients with a pincer deformity had a relative risk of 2.0 of having the same deformity (43 of 116 sibling hips versus 29 of 154 control hips, p = 0.001). Bilateral deformity occurred more often in the siblings (42 of 96 siblings versus 13 of 77 control subjects, relative risk 2.6, p = 0.0002). The prevalence of clinical features in those hips with abnormal morphology was also greater in the sibling group compared with the control group (41 of 109 sibling hips versus 7 of 46 control hips, relative risk 2.5, p = 0.007). In 11 sibling hips there was grade-2 osteoarthritis according to Kellgren and Lawrence versus none in the control group (p = 0.002).

Genetic influences are important in the aetiology of primary femoroacetabular impingement. This risk appears to be manifested through not only abnormal joint morphology, but also through other factors which may modulate progression of the disease.

Femoroacetabular impingement (FAI) is an important cause of pain in the hip in young adults and represents a mechanism by which abnormal joint morphology can lead to osteoarthritis (OA).[1,2] A number of conditions predispose to FAI such as slipped capital femoral epiphysis (SCFE)[3] and Perthes' disease, but in most cases there is no history of previous hip pathology.[1,4-6] The condition may therefore be considered as primary or idiopathic. In addition to uncertainty as to the cause of the deformity in primary FAI, clinical experience suggests that patients presenting with other complaints sometimes have evidence of FAI, but without symptoms or evidence of OA, indicating that other factors such as the durability of the labral-chondral complex and the level of activity of the individual may modulate progression of the disease.

Genetic factors are important in the aetiology of common musculoskeletal disorders such as tears of the rotator cuff[7] and OA of the hip[8-12] and knee.[9,13,14] In the hip, it is possible that some of the genetic predisposition to OA is manifested through abnormal joint morphology and it may be that FAI itself has an underlying genetic predisposition. Currently, our understanding of why FAI occurs and how best to treat it is modest. The identification of those at risk of developing symptomatic FAI will allow the natural history of the condition to be studied, facilitate development of biomarkers of progression and response to treatment, and potentially lead to recruitment for clinical trials. In the longer term, improved understanding of basic pathological mechanisms may provide direct clinical benefits to patients.

Our aim was to establish the importance of genetic factors in the aetiology of FAI by clinical and radiological investigation of the siblings of patients diagnosed with FAI in comparison with a control group.

Patients and Methods

The siblings of patients (probands) treated for FAI were recruited and examined for evidence of FAI. The control group consisted of the spouses or partners of the probands and the siblings. The relative risk for the condition in

the sibling was then calculated by dividing the incidence in the siblings by the incidence in the control group. By this calculation conditions with no genetic association have a relative risk of one, and those with a genetic predisposition a relative risk greater than one.

Identification of proband. The study had ethical approval. Probands were recruited from three centres which routinely performed surgery for FAI by arthroscopy, anterior arthrotomy, or surgical dislocation. Clinical and radiological criteria were applied to validate the diagnosis of FAI among the probands. The proband had to have a clinical diagnosis of anterior FAI and a positive anterior impingement test[15] documented in the initial clinical correspondence. Then, the patient had to have an anteroposterior (AP) radiograph of the pelvis in the supine position with the x-ray beam centred in the midline and on the point midway between the superior border of the pubic symphysis and a line drawn connecting the anterior superior iliac spines,[16,17] and a cross-table lateral radiograph of the hip taken in 15° of internal rotation.[16,18,19]

The following exclusion criteria were applied to ensure that only probands with primary anterior FAI were recruited to the study. Patients had to be between the ages of 18 and 55 years and not have a diagnosis of posterior FAI. They should not have had previous investigation of or treatment to either hip as a child or adolescent, or have had acquired FAI before or after skeletal maturity (for example secondary to SCFE, trauma or infection), as determined from the case notes. Those undergoing a surgical dislocation who were found to have advanced disease and had a resurfacing arthroplasty performed at the initial procedure were excluded, as were patients with definite radiological OA of the hip equivalent to grade 2 of the classification of Kellgren and Lawrence.[20] Patients with acetabular dysplasia as diagnosed by a lateral centre-edge angle on the AP radiograph of less than 20°,[16,21] were also excluded as were those of non-Caucasian origin to eliminate confounding because of racial variation. Finally, the obturator-foramen index[22] was measured on all the AP pelvic radiographs to ensure that there was no significant pelvic rotation. Only patients with an index between 0.7 and 1.4 were accepted in the study.[23]

Probands were identified both prospectively and retrospectively from a database. They were asked to detail siblings resident in the United Kingdom, and their spouse or partner. In addition, to validate the information from the case notes, the probands were asked whether they had been investigated or treated for problems with either hip as a child, adolescent or adult. All the probands had prospectively completed the Oxford hip score[24] (OHS) and the non-arthritic hip score pre-operatively. The OHS is validated, patient-based, sensitive to clinically important change and scored from 0 (asymptomatic) to 48 (most severe symptoms).[25] The non-arthritic score is validated, patient-based and scored from 0 (asymptomatic) to 100 (most severe symptoms).[26]

Recruitment and assessment of the siblings and control group. Siblings and control subjects were invited to participate in the study. In order to increase the number of the latter, all participating siblings were asked to detail their spouses or partners. All participating subjects were then assessed in a dedicated research clinic by a single experienced observer (TCBP).

The clinical assessment included a history, examination and completion of the OHS and non-arthritic hip score for each hip and the UCLA (University of California, Los Angeles) activity score.[27] The last is scored from 0 to 10, is validated and incorporates occupation and sporting activity.[27,28] A proforma facilitated standardisation of the clinical assessment. All the subjects were asked whether they had previously had surgery on either hip, undergone investigation of or treatment for pain in the hip as a child or adolescent, had experienced any groin pain or clicking on either side in the last two years and whether either of their parents had undergone total hip replacement or resurfacing arthroplasty for OA. A routine examination of the hips was performed and the presence of a positive anterior impingement sign or irritability of movement of the hip recorded.

All participants had an AP radiograph of the pelvis in the supine position and a cross-table lateral radiograph of each hip taken as described above, using a 15° wedge placed beneath the femoral condyles to standardise rotation. The radiographer repeated the AP radiograph of the pelvis if necessary to ensure that the obturator foramen index was within 0.7 and 1.4.

Radiological measurement. There are two principal mechanisms of FAI, namely, cam and pincer.[1,2] Cam impingement is characterised by a reduction of offset or abnormal asphericity at the anterolateral femoral head-neck junction. Pincer impingement results from over-coverage of the femoral head by the acetabulum, which may be global (coxa profunda) or focal (cranial retroversion of the acetabulum). Most patients have combined cam and pincer morphology and are described as having 'mixed FAI'.[1,2] Based on the radiological measurements described below, the presence of cam and pincer deformities in the probands, siblings and the control group was recorded and their morphology classified as being normal, pure cam, pure pincer or mixed.

Proximal femoral morphology. From the cross-table lateral radiograph, the alpha angle[16,29-31] and anterior offset ratio[16,18,31,32] were measured by saving the digital images as TIFF files, which were then analysed in a custom-designed software program in Matlab version R2007a (The Mathworks Inc, Natick, Massachusetts). The accuracy of this program had been tested and confirmed during its development.[31] Based on a previous study from our institution of 157 normal subjects using the same standardised radiological and measurement technique,[31] 95% reference intervals[33] for the alpha angle and anterior offset ratio were calculated and a cam deformity was defined as an alpha angle > 62.5° or an anterior offset ratio < 0.135.

Acetabular morphology was determined from the AP radiograph of the pelvis. Global overcoverage is suspected when the hip has coxa profunda or protrusio.[2] Because of its high prevalence in normal hips, especially in women,[34] we defined coxa profunda based on the measurement of the lateral centre-edge angle,[16,21] the acetabular index,[16,35] and the acetabular depth-to-width ratio.[36,37] Because there is limited evidence for the thresholds of abnormality for these measurements in the context of pincer FAI,[16,38,39] we calculated 95% reference intervals[33] from the control subjects who had no evidence of OA and were asymptomatic with a normal examination. There were 23 such men and 23 women. Global overcoverage was thus defined as a lateral centre-edge angle > 38.0° (men and women) or an acetabular index < -3.7° (men) or < -4.9° (women), or an acetabular depth-to-width ratio of > 0.55 (men) or > 0.64 (women) or coxa protrusio.[2] All the measurements were made from the TIFF files using the Matlab software program.

Focal overcoverage was diagnosed by the presence of a crossover sign.[16,40] Because of the sensitivity of this assessment to pelvic tilt,[16,41] we measured the distance from the sacrococcygeal joint to the pubic symphysis and only recorded the crossover sign if this distance was within 40 mm to 55 mm for women and 25 mm to 40 mm for men.[41,42] The distances were measured using the Picture Archiving and Communication System (PACS, 2004; GE Healthcare UK Ltd, Little Chalfont, United Kingdom). Assessment of global overcoverage was made in all subjects regardless of the sacrococcygeal joint-pubic symphysis distance, since it was considered that referencing the margins of the sourcil[16] rather than the outermost point of the acetabular rim[21] would protect against error due to variation in pelvic tilt.[23] A pincer deformity was diagnosed if there was either focal or global overcoverage or both.

Presence of osteoarthritis. Osteophytosis was graded using an atlas[43] and the minimum width of the joint-space recorded in each hip. Narrowing of the joint space was defined as a minimum width of < 2.80 mm in men and < 2.87 mm in women.[31] An overall grade of OA was assigned using the system of Kellgren and Lawrence,[20] whereby grade-2 is defined as definite but mild OA, with narrowing of the joint space and osteophytosis.

Observer variability. All the measurements were made by one observer (TCBP). Intraobserver repeatability was obtained by the re-measurement of 20 sets of radiographs (40 hips) after an interval of four weeks. Interobserver reproducibility was obtained by a second observer (MRW) measuring the same 20 sets of radiographs.

Power analysis. The sibling relative risk for OA of the hip is approximately 2.[8,10,11] The incidence of morphology of FAI and its clinical features in the general population is unknown. Assuming a similar sibling risk for abnormal morphology, with an estimation of the prevalence of abnormal morphology in the general population of 20%, then the prevalence in the siblings would be 40%. On this basis, to achieve 80% power (alpha 0.05), the estimated sample size in each group was 82 subjects.

Statistical analysis. The one-sample Kolmogorov-Smirnov test was used to confirm a Gaussian distribution of the measurements for global overcoverage in the normal control subjects. Differences in continuous variables between groups and genders were compared using the unpaired t-tests. The chi-squared test and Fisher's exact test were used to determine variations in the prevalence of abnormal morphology, clinical features and OA between groups. Intra- and inter-observer reliability of numerical data was assessed by intra- and interclass coefficients and of categorical data by the kappa coefficient. All the statistical calculations were performed using SPSS version 13.0 software (SPSS Inc., Chicago, Illinois). A p-value ≤ 0.05 was deemed to be significant.

Results

We identified 230 probands who were eligible for the study. Of these, 99 did not reply and 14 refused to participate. From the remaining 117, 73 had siblings resident in the United Kingdom and 64 of these ultimately provided siblings for the study. The clinical details and diagnoses of the probands are shown in Table I. The distribution of the type of FAI by gender is similar to that of published series.[2,4,38] Of the 64 patients, 28 of the 30 men and 33 of the 34 women had been treated surgically. There were 96 siblings and 77 control subjects. The sibling group comprised 54 men and 42 women with a mean age of 37.9 years (19 to 63) and a mean UCLA activity score of 8.5. The control group comprised 39 men and 38 women with a mean age of 41.8 years (22 to 65) (p = 0.019) and a mean UCLA activity score of 8.0 (p = 0.086).

Seven siblings reported childhood symptoms, but only one had treatment, by an osteotomy for Perthes' disease. A further sibling had incidental radiological evidence of Perthes' disease of grade 3 of the classification of Stulberg, Cooperman and Wallensten.[44] Three control subjects reported childhood symptoms, but only one had received treatment, with a hip spica for developmental dysplasia.

Hip morphology. Table II summarises the morphological classification of each hip in the sibling and control groups. The prevalence of a cam deformity in the siblings of those probands with a cam deformity was significantly greater than that in the control group (p < 0.001, Table III).

The presence of focal acetabular cover (a crossover sign) was not assessed in 28 female (56 hips) and 19 male (38 hips) control subjects, and in 26 female (52 hips) and 23 male (46 hips) siblings because the sacrococcygeal joint-pubic symphysis distance was outside the acceptable range. Assessment of global overcoverage was still made in these subjects. The prevalence of a pincer deformity in the siblings of those probands with a pincer deformity was significantly higher than that in the control group (Table IV). The prevalence of bilateral FAI morphology was higher among the siblings (42 of 96 siblings *versus* 13 of 77 control subjects, relative risk 2.6, p = 0.002). Overall, 16 of 77 (20.8%) control subjects

T. C. B. POLLARD, R. N. VILLAR, M. R. NORTON, E. D. FERN, M. R. WILLIAMS, D. W. MURRAY, A. J. CARR

Table I. Clinical details and diagnoses of the 64 probands providing siblings for the study

| | | | FAI* classification | | |
| | | | Pure cam (%) | Mixed (%) | Pure pincer (%) |
Gender	Number	Mean age (yrs)			
Male	30	34.4 (18 to 54)	14 (*46.7*)	16 (*53.3*)	0 (*0.0*)
Female	34	38.6 (19 to 55)	9 (*26.5*)	13 (*38.2*)	12 (*35.3*)

* FAI, femoroacetabular impingement

Table II. Summary of morphological classification for each hip in the sibling and control groups

| | | | | Morphological classification | | | |
Group	Gender	Number	Hips	Normal (%)	Pure cam (%)	Mixed (%)	Pure pincer (%)
Control	Male	39	78	53 (*67.9*)	12 (*15.4*)	2 (*2.6*)	11 (*14.1*)
	Female	38	76	55 (*72.4*)	5 (*6.6*)	4 (*5.3*)	12 (*15.8*)
Siblings	Male	54	108	41 (*38.0*)	33 (*30.6*)	16 (*14.8*)	18 (*16.7*)
	Female	42	84	42 (*50.0*)	15 (*17.9*)	5 (*6.0*)	22 (*26.2*)

Table III. Prevalence and relative risks of a cam deformity in the siblings of those probands with a cam deformity. Brothers are compared with male control and sisters with female control subjects. The 95% confidence interval is given in parentheses

| | Brother | | | Sister | | | All siblings | | |
Proband	Prevalence (hips)	Relative risk	p-value	Prevalence (hips)	Relative risk	p-value	Prevalence (hips)	Relative risk	p-value
Male	31/54	3.2 (1.9 to 5.4)	< 0.001	11/36	2.6 (1.2 to 5.7)	0.032	42/90	3.1 (2.1 to 4.8)	< 0.001
Female	18/44	2.3 (1.3 to 4.1)	0.009	6/26	1.9 (0.8 to 4.9)	0.196	24/70	2.3 (1.4 to 3.8)	0.001
All	49/98	2.8 (1.7 to 4.7)	< 0.001	17/62	2.3 (1.1 to 4.8)	0.028	66/160	2.8 (1.8 to 4.2)	< 0.001

Table IV. Prevalence and relative risks of a pincer deformity in the siblings of those probands with a pincer deformity. Brothers are compared with male control and sisters with female control subjects. The 95% confidence interval is given in parentheses

| | Brother | | | Sister | | | All siblings | | |
Proband	Prevalence (hips)	Relative risk	p-value	Prevalence (hips)	Relative risk	p-value	Prevalence (hips)	Relative risk	p-value
Male	5/24	1.3 (0.5 to 3.2)	0.760	6/20	1.4 (0.6 to 3.2)	0.387	11/44	1.3 (0.7 to 2.4)	0.397
Female	15/34	2.6 (1.4 to 4.9)	0.004	17/38	2.1 (1.2 to 3.7)	0.015	32/72	2.4 (1.6 to 3.6)	< 0.001
All	20/58	2.1 (1.1 to 3.8)	0.025	23/58	1.9 (1.1 to 3.2)	0.022	43/116	2.0 (1.3 to 3.0)	0.001

had at least one hip with a cam deformity compared with 45 of 96 siblings (46.9%) (relative risk = 2.3, p < 0.001). Of the 77 control subjects, 22 (28.6%) had at least one hip with a pincer deformity compared with 39 of the 96 (40.6%) siblings (relative risk = 1.4, p = 0.111).

Clinical features and morphology of FAI. The prevalence of clinical features in the siblings with abnormal morphology was significantly higher, particularly in men, and was statistically significant because of the magnitude of the relative risks in spite of the small numbers (p = 0.040 Table V). Table VI shows the pre-operative hip scores in the probands and symptomatic siblings. Six siblings had hip scores which were worse than the means for the probands.

Potentially these findings could be explained by the deformity being more severe in those siblings with FAI morphology compared to the control subjects with FAI morphology. However, the prevalence of a mixed pattern of FAI was similar in these subgroups (21 of 109 siblings

hips *versus* 6 of 46 control hips, p = 0.487, Table II). Furthermore, the mean alpha angle and anterior offset ratios were not significantly different in those siblings and controls with cam deformities (p = 0.578 and p = 0.320 respectively).

Because of the potential confounding effect of the level of activity on the likelihood of an individual with FAI morphology having clinical features, the siblings with the morphology and signs of FAI were compared with the control subjects with FAI morphology without signs for age and level of activity (Table VII).

Osteoarthritis. In the sibling group, 11 of 96 siblings (5 unilateral, 3 bilateral) had grade-2 OA compared with 0 of 77 control hips (p = 0.002). In no case was OA more advanced than grade 2.[19] Of the 64 proband families 13 had at least one parent who had undergone a hip replacement for OA, compared with six of the 77 control families (p = 0.046).

Table V. Prevalence and relative risks of clinical features in the siblings and control subjects with femoroacetabular impingement morphology. The 95% confidence interval is given in parentheses

Clinical feature	Male hips				Female hips				All hips			
	Siblings	Control subjects	Relative risk	p-value	Siblings	Control subjects	Relative risk	p-value	Siblings	Control subjects	Relative risk	p-value
Signs	28/67	2/25	5.2 (1.3 to 20.3)	0.002	13/42	5/21	1.3 (0.5 to 3.2)	0.768	41/109	7/46	2.5 (1.9 to 5.9)	0.007
Symptoms and signs	9/67	0/25	-	0.107	6/42	1/21	3.0 (0.4 to 23.3)	0.408	15/109	1/46	6.3 (0.9 to 46.5)	0.040

Table VI. The mean OHS[*] and NAHS[†] for the probands pre-operatively and siblings with symptoms and signs

Group	Number	Mean OHS (range)	Mean NAHS (range)
Probands	64	28.6 (11 to 47)	58.9 (23 to 99)
Siblings	15	36.6 (22 to 47)	76.6 (44 to 100)

* OHS, Oxford hip score

† NAHS, non-arthritic hip score

Table VII. Comparison of the mean age (years) and mean activity level (UCLA[*] activity score) in the siblings with femoroacetabular impingement (FAI) morphology and clinical signs, and the control subjects with FAI morphology but no clinical signs

Gender	Group	Number	Number of hips	Mean age (yrs)	p-value	Activity level	p-value
Males	Siblings	18	28	38.6 (19 to 58)		9.0	
	Controls	17	23	44.9 (30 to 65)	0.129	7.9	0.019
Females	Siblings	10	13	36.9 (22 to 60)		7.4	
	Controls	12	16	42.9 (24 to 52)	0.223	7.6	0.743

* UCLA, University of California, Los Angeles

Patients with cam FAI often present with a distinct 'bump' at the femoral head-neck junction. Because there have been no longitudinal observational studies of patients with FAI before presentation, the reasons for the development of these bumps are unknown. Three unrelated individuals with cam morphology in the sibling group had clear erosive lesions at the head-neck junction. It is possible that a reactive phenomenon results in bony deposition at these sites, with a resultant bump which exacerbates the cam deformity. Figure 1 illustrates this in a family of three brothers.

Reliability. Inter- and intraobserver reliability data are presented in Table VIII.

Discussion

Since the concept of FAI was introduced,[1,2] a change in the management of the young adult hip has occurred in conjunction with advances in surgical techniques. Improved understanding of the basic science of FAI will further advance knowledge of the pathological mechanisms and ultimately enhance treatment.

The cause of the cam deformity in primary FAI is unknown. Because a similar deformity occurs in SCFE and Perthes' disease, it has been suggested that a subclinical event occurs during development.[1] Alternatively, the deformity may represent an abnormal extension from the epiphysis.[45] Our study has indicated that either the deformity is determined at conception or that there is a genetic predisposition to abnormal development or subclinical hip disease before skeletal maturity. There is evidence for a genetic predisposition to clinically evident SCFE,[46] which may support the latter concept, but the evidence in Perthes' disease is less clear.[47-49] The high prevalence of cam deformity in the siblings in the absence of clinical features and OA suggests that the deformity is a primary, not secondary, phenomenon. The presence of erosions at the head-neck junction in young cam hips was intriguing. We suggest that the primary cam deformity gradually worsens over time, with a 'bump' growing as a consequence of reactive bony deposition. A longitudinal study is required to validate these cross-sectional observations in these groups and, if possible, to extend the study to their offspring before skeletal maturity occurs.

With regard to the acetabulum, the importance of genetic factors in the aetiology of dysplasia[50,51] and primary protrusio[52,53] is well recognised. The sibling risks for pincer morphology were significant although less striking and the gender of the proband appeared to be more important than for the cam deformity. Up to one-sixth of the male sibling and control hips had pure pincer morphology (Table II),
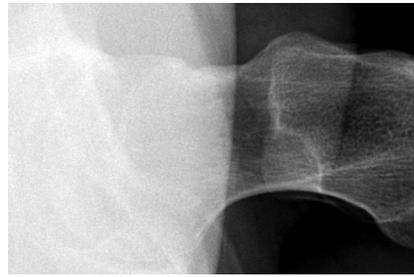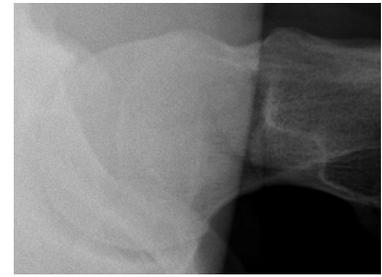
Fig. 1a

Fig. 1b

Fig. 1c

Radiographs of three brothers with different stages of clinical and radiological progression showing a) a pre-operative view in a 27-year-old proband with an alpha angle of 81.3°, b) normal clinical examination in a 21-year-old brother with an alpha angle of 63.1° and an erosive lesion at the head-neck junction and c) positive impingement sign in a 23-year-old brother with an alpha angle of 78.8° and bony deposition at the head-neck junction forming a bump.

Table VIII. Reliability of the radiological morphological measurements. Values of agreement between 0.61 and 0.80 are considered 'good' and between 0.81 and 1.0 as 'very good'[59]

Measurement	Interobserver reproducibility	Intraobserver repeatability
Alpha angle	0.84	0.91
Anterior offset ratio	0.73	0.75
Lateral centre-edge angle	0.78	0.96
Acetabular index	0.81	0.92
Acetabular depth-width ratio	0.90	0.97
Crossover sign	0.62	0.78

but none of the male probands were in the pure pincer group which questions the significance of pure pincer morphology in men. In addition, the lack of significantly higher relative risks for pincer deformity when the proband was male with mixed FAI (Tables I and IV) suggests that men with cam FAI acquire pincer deformities as a secondary phenomenon, as a result of repeated microtrauma to the labrum with resultant ossification and overcoverage. This may account for the fact that the prevalence of pincer morphology in the siblings of male probands with mixed FAI was slightly higher than one, because most are yet to develop the secondary deformity. In women with FAI, the primary deformity is more likely to be pure pincer (Table I) and therefore their siblings are prone to have the same morphology (Table IV).

Genetic influences have been shown to be important in the aetiology of OA of the hip,[8-12] but studies have been limited because they were not designed to determine how much of this risk was attributable to poor 'cartilage biology' and how much to mechanical factors secondary to deformity. The genetic predisposition to OA has joint specificity,[9,10] suggesting that local factors are important. However, abnormal morphology of the hip does not inevitably result in OA.[54,55] Progression of the disease in FAI is likely to be modified by the level of activity and injury to the labral-chondral complex. Our patients with FAI morphology and clinical features had probably developed labral tears or pathology at the labral-chondral junction, and further assessment using MRI would have been useful. The

increased sibling risk for clinical features given an abnormal morphology suggests that there is an additional genetic component, beyond the increased risk of abnormal morphology, involved in the development of progressive disease. Our data did not support the notion that the increased incidence of clinical features was due to more severe deformity in the siblings than controls with FAI morphology. The increased prevalence of OA in the siblings and of replacement in their parents supports this concept, which may be extended to explain the relatively common finding of FAI morphology in the general asymptomatic population, as in the control subjects, and the fact that not all patients with cam deformities progress.[54] The higher level of activity of the male siblings may confound these observations to a degree, but is unlikely to nullify them.

Our study has a number of strengths and weaknesses. The strengths were the power and the fact that all subjects had clinical and radiological screening of their hips, whether symptomatic or not. Had this not been the case, the subclinical prevalence of abnormal morphology and positive findings on examination would have been missed. The inherent weaknesses of a sibling study include the quality of matching of the control group with regard to environmental factors and ascertainment bias. The control subjects were slightly older, but the overall level of activity was similar and the higher proportion of men in the sibling group was adjusted for by gender-specific comparison. Ascertainment bias refers to the selection and assessment of participants. Siblings with symptomatic hips would be more likely

to participate, but this self-selection bias would also apply to the control subjects and should not have affected relative risk calculations significantly. The study endpoints were the identification of clinical and radiological abnormalities. Ideally, the assessor should have been blinded to participant status, but this was not practically possible. Plain radiography was used to assess the morphology of the joint. Radiography is practical because it is cheap, fast, and does not require specialist radiological interpretation. From the participants' perspective, although there is a small dose of ionising radiation, it is otherwise of minimal inconvenience and provides the opportunity for instant feedback from the researcher. This is important when it is considered that their siblings (the probands) have undergone major surgery at a young age. Radiography is limited in comparison with CT[56] or MRI because FAI is a three-dimensional condition. However, the method used in our study is recommended as a screening tool because it identifies the important underlying bony abnormalities, with the exception of retroversion of the femoral neck, upon which a diagnosis of FAI may be made.[2,16,38] The cross-table lateral radiograph is validated for the assessment of cam deformity.[19,31] The triangular index, assessed on plain radiography has been suggested as an indicator of cam impingement.[57] The AP pelvic radiograph requires careful standardisation,[16,23,38] a principle to which we adhered. The calculations of observer variability demonstrated good reliability of measurement. Robust definitions of normality and abnormality based on these measurements are lacking and therefore by necessity our thresholds were derived from normal subjects,[33] although all the probands had a definite abnormality based on these definitions. The prevalence of deformity in the study group will be determined by the threshold set, but marginal variation is unlikely to alter the relative risks significantly. Concerns remain regarding screening for acetabular retroversion, because of the uncertainty as to how to deal with pelvic tilt. Correction to a neutral pelvic tilt using either CT or the use of simultaneous lateral pelvic radiography[59,60] may facilitate measurement, but the functional position of an individual's pelvis, and the position of the acetabulum, will not necessarily equate with a neutral pelvic tilt. Therefore correction may not be appropriate since whether change occurs in pelvic tilt when moving from the standing to the supine position is controversial.[61] Because of these concerns, we only assessed local overcoverage if the pelvic tilt was within the published normal range.[41,42] Unsurprisingly, this led to the exclusion of this assessment for many subjects,[62] which may have introduced bias. Finally, we used the UCLA activity score which was developed in the 1980s for patients undergoing hip replacement. Of the participants in our study 73% had a UCLA score of at least eight, which effectively changes it from a ten-point score to a three-point score in our series. More precise methods of the assessment of activity are required for young patients undergoing surgery to the hip joint.

Our study has shown that genetic factors are important in the aetiology of FAI, acting through both the joint morphology and through biological factors which affect progression of the disease. We observed a spectrum of disease, ranging from abnormal morphology without clinical features, through clinically evident FAI, to OA. At-risk cohorts may now be identified which will provide the opportunity for the study of the development of the deformity, its natural history and progression. In addition, the identification of subjects suitable for evaluating biomarkers and recruitment into clinical trials is facilitated. The success of these studies will need consensus on the optimum method of assessment of morphology and activity. This, together with the improved understanding of the function and degeneration of the labral-chondral complex, will accelerate the development of techniques for joint preservation.

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