The genetic contribution to hip joint morphometry and relationship to hip cartilage thickness

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Summary
A twin study approach was used to explore the genetic determinants of hip joint morphometry and their relationship to hip cartilage thickness. Our analysis used data on anthropometric characteristics and radiographic features of a group of 222 monozygotic (MZ) and 240 dizygotic (DZ) twins. We confirmed that genetic factors account for most of the variation in minimal joint space (MJS) and acetabular anatomy. This genetic variation was largely due to factors unique to MJS itself and not explained by arthropometric variables or measurements of acetabular morphology. Only a small proportion was shared with genetic factors underlying acetabular shape, mainly the centre edge angle.

Introduction and summary
Acetabular dysplasia has been implicated in the development of osteoarthritis (OA) of the hip joint particularly in women. We have recently shown that genetic factors account for the majority of the population liability to hip OA. Specifically minimal joint space (MJS)—which is a surrogate for cartilage thickness and the best radiological indicator of hip OA in epidemiological studies—has a heritability of 64%.

In this study our aim was to assess whether the genetic variation in minimal joint space (MJS) might be accounted for by genetic factors that also determine hip morphology.

Methods, results and discussion
STUDY POPULATION
The analysis used data from the St Thomas’ U.K. Adult Twin Registry, consisting of unselected volunteers, recruited through successive national media campaigns. A random sample of white, female twins, over 40 years of age were selected. The 462 twins eligible for inclusion in the present study had no history of chronic bone or joint disease other than osteoarthritis (OA) and were representative of the normal U.K. population. The data included anthropometric and lifestyle variables collected through both a nurse-administered questionnaire and clinical examination. Zygosity was determined by a standard questionnaire and confirmed when necessary by multiplex DNA fingerprinting.

RADIOGRAPHIC ASSESSMENT
Pelvic radiographs were obtained in supine antero-posterior position with a standard tube to film distance of 100 cm and the feet positioned in 15° of internal rotation.

All films were assessed for the following standard radiographic features: minimal joint space, center–edge angle and acetabular depth (Fig. 1). The center of each femoral head was established by superimposing a circle around its margin. The minimal joint space (MJS) was measured in mm, along a radius from the center of the femoral head, and defined as the shortest distance found from the femoral head to the acetabulum. The center–edge angle was defined as the angle between a line joining the center of the femoral head to the lateral margin of the acetabular roof and a line perpendicular to that joining the centers of the two femoral heads. The lateral acetabular margins were distinguished from acetabular osteophytes, if present. Acetabular depth was defined as the greatest perpendicular distance from the acetabular roof to a line joining the lateral margin of the acetabular roof and the upper corner of the symphysis pubis on the same side. Low values of acetabular depth and center–edge angle reflecting an abnormally shallow and abnormally laterally displaced acetabulum characterize acetabular dysplasia.

REPRODUCIBILITY
The pelvic radiographs were read by two readers who were blinded to the pairing and the zygosity of the twins. Repeatability was examined in a subgroup of random twin’s pelvic X-rays. Their interobserver and intraobserver agreement as assessed by kappa statistic using different cut-off levels exceeded 0.7.
For any continuously distributed trait, the variance measured at the population level has contributions from both genetic and environmental components. The twin model allows this variation to be separated into additive genetic (A) and dominance (D) genetic components, and into environmental variation accounted by the twins common environment (C) (i.e. shared by members of the twin pair, such as diet), and environmental variation that is unique to each twin (E). By simultaneously examining data from multiple correlated variables, the method can be extended to assess the extent to which these components of variation are shared between variables. The coefficients from the model provide a direct measure of the shared genetic and environmental covariance (and hence correlation) between phenotypes. In the analysis MJS, center–edge angle, acetabular depth, height and weight were all included in the multivariate model; the effects of age were taken into account through linear regression. Variance components, and genetic and environmental correlations were estimated from the parameters of the model that provided the most parsimonious explanation of the data selected by standard backwards elimination rules using a threshold of \( P=0.05 \) for retaining variables.

RESULTS

Pelvic X-rays of 111 MZ and 120 DZ twin pairs were studied. The analysis was confined to data from the right hip. The twins' characteristics are shown in Table I. There was no significant difference in any of the variables between MZ and DZ twins. The mean values of MJS, center–edge angle and acetabular depth are similar to those of previous studies. Twenty-one out of 462 twins (4.6%) had MJS less than 2.5 mm and nine (2%) had severe narrowing of the joint space <1.5 mm. Ninety twins (19.7%) had center–edge angles less than 30° and 22 (4.8%) less than 25°. Abnormally shallow acetabulum, less than 9 mm, was found in 17 (3.7%) twins.

The model selected to show the best fit to the data contained only additive genetic variance (A) and unique environmental variance (E). Table I shows the heritabilities from this model. As expected, height and weight are highly heritable. MJS, center–edge angle and acetabular depth also have a strong genetic influence ranging between 59 and 62%.

Negative phenotypic correlations were observed for MJS and center–edge angle (\( r = -0.33 \)) and MJS and acetabular depth (\( r = -0.14 \)), and are similar to those reported in previous epidemiological studies. The genetic and environmental correlations between each of the variables derived from parameter estimates of the best fitting AE model are shown in Table II. Genetic correlations between the radiographic variables were higher than environmental correlations.

### Table I

<table>
<thead>
<tr>
<th>Variables</th>
<th>MZ (N=222)</th>
<th>DZ (N=240)</th>
<th>Heritability (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MJS in mm (S.D.)</td>
<td>3.7 (0.9)</td>
<td>3.8 (0.8)</td>
<td>0.62 (0.50, 0.71)</td>
</tr>
<tr>
<td>CEA in degrees (S.D.)</td>
<td>34.5 (6.8)</td>
<td>34.9 (6.1)</td>
<td>0.62 (0.51, 0.71)</td>
</tr>
<tr>
<td>ADP in mm (S.D.)</td>
<td>13.1 (2.9)</td>
<td>13.3 (2.8)</td>
<td>0.59 (0.47, 0.69)</td>
</tr>
<tr>
<td>Mean height in cm (S.D.)</td>
<td>161.3 (5.8)</td>
<td>161.7 (5.9)</td>
<td>0.82 (0.76, 0.87)</td>
</tr>
<tr>
<td>Mean weight in kg (S.D.)</td>
<td>63.3 (10.1)</td>
<td>64.5 (10.6)</td>
<td>0.67 (0.57, 0.75)</td>
</tr>
<tr>
<td>Mean age in years (range)</td>
<td>58.2 (43,70)</td>
<td>57.3 (42,70)</td>
<td></td>
</tr>
</tbody>
</table>

*CEA: center–edge angle; ADP: acetabular depth.

### Table II

<table>
<thead>
<tr>
<th></th>
<th>MJS</th>
<th>CEA</th>
<th>ADP</th>
<th>HT</th>
<th>WT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MJS</td>
<td>-0.4622</td>
<td>-0.0474</td>
<td>0.0527</td>
<td>0.1248</td>
<td>-0.0495</td>
</tr>
<tr>
<td>CEA</td>
<td>-0.2431</td>
<td>-0.0871</td>
<td>0.1535</td>
<td>0.0940</td>
<td>0.1150</td>
</tr>
<tr>
<td>ADP</td>
<td>-0.0031</td>
<td>-0.0912</td>
<td>-0.0458</td>
<td>0.3044</td>
<td></td>
</tr>
<tr>
<td><strong>HT</strong></td>
<td><strong>0.1393</strong></td>
<td><strong>-0.0871</strong></td>
<td><strong>0.1535</strong></td>
<td><strong>0.0940</strong></td>
<td><strong>0.1150</strong></td>
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<tr>
<td><strong>WT</strong></td>
<td><strong>-0.0031</strong></td>
<td><strong>-0.0912</strong></td>
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<td><strong>0.3044</strong></td>
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</tbody>
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*CEA: center–edge angle; ADP: acetabular depth.

Genetic and environmental correlations derived from the best fitting multivariate model. The genetic correlations are shown in the lower triangle, while the environmental are in the upper.
In the variance components analysis 45.7% of the variation in MJS was due to genetic factors that were unique to MJS and 12.2% of the genetic variation was shared with center–edge angle. Acetabular depth, weight and height accounted for only 3.3% of the genetic variance observed. The environmental variance unique to MJS was 34.9%, whereas the remaining variables accounted for 1.1% of the variance. Age contributed 2.8% to the model.

**DISCUSSION**

A number of reports and clinical trials have implicated mild developmental anatomical abnormalities—especially acetabular dysplasia in women—as predisposing factors to premature hip OA. Subsequent cross-sectional epidemiological studies have generally failed to support this association. However, a recent prospective population-based study reported that mild acetabular dysplasia was associated with a modest increased risk of incident hip OA in elderly white women.

Radiographic hip OA and particularly MJS are predominantly genetically determined. We designed this study to investigate whether MJS has genetic determinants in common with the radiographic measurements of acetabular morphology: center–edge angle and acetabular depth or anthropometric variables such as height and weight. In addition to MJS, we found that center–edge angle and acetabular depth were highly heritable. The genetic variance in MJS was mostly unique and did not appear to have major genetic determinants in common with any of the anthropometric or radiographic measurements of acetabular morphology examined. Only 12% of its genetic variation was shared with center–edge angle. These observations are consistent with the view that mild aberrations in acetabular morphology are unlikely to explain the distribution of hip OA in the general population.

For all variables, genetic as opposed to environmental factors were the major source of variation. Environmental correlations between the variables were weak. The statistically significant genetic correlations between MJS and center–edge angle and MJS and acetabular depth were negative and also do not support the notion of acetabular dysplasia being a risk factor for the development of hip OA in the general population.

Possible sources of MJS genetic variation may include common genetic determinants with other structures such as bone and cartilage. Shared genetic factors may exist between hip OA and high bone mass. Preliminary genetic linkage data in OA have implicated chromosomal regions encoding genes of potential structural importance such as cartilage matrix component.

In conclusion, MJS, a surrogate of cartilage thickness and radiographic indicator of hip OA, is predominantly genetically determined, as is acetabular anatomy. Only a small proportion of the genes influencing these traits is shared. Overall, our data did not support a role for common genes controlling acetabular dysplasia and the presence of radiographic hip OA in the female population.

**References**