HERITABILITIES OF RADIOLOGIC OSTEOARTHRITIS IN PERIPHERAL JOINTS AND OF DISC DEGENERATION OF THE SPINE

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Objective. To estimate the genetic influence on the occurrence of radiologic osteoarthritis (ROA) in the knees, hips, and hands and disc degeneration of the spine in the general population.

Methods. A random sample of 1,583 individuals was drawn to estimate the prevalence of ROA and disc degeneration in the general population. Of 118 probands with multiple affected joint sites who were derived from this sample, we were able to recruit 257 siblings. The variance of ROA and disc degeneration within sibling pairs was compared with the variance between sibling pairs. Heritability estimates for ROA in the knees, hips, and hands and for disc degeneration of the spine were calculated. OA was defined according to radiologic criteria, using the Kellgren/Lawrence grading system.

Results. We observed that hand ROA and disc degeneration of the spine were statistically significantly more frequent in siblings than in the random sample, whereas the prevalence of knee and of hip ROA was similar and lower, respectively. Heritability estimates for hand ROA and disc degeneration were statistically significant, $P = 0.56$ (95% confidence interval [95% CI] 0.34–0.76) and $P = 0.75$ (95% CI 0.30–1.00), respectively. For knee and hip ROA, no evidence of a genetic effect in the general population was found. Finally, the heritability estimate for a score that summed the number of joints affected in the knees, hips, hands, and spine was 0.78 (95% CI 0.52–0.98). All heritability estimates were adjusted for age, sex, body mass index, and bone mineral density.

Conclusion. The present study shows that in the general population, there is a strong genetic effect for hand ROA and disc degeneration of the spine. The findings on the total number of joints affected at multiple sites suggest genetic susceptibility to generalized OA.

A genetic effect on osteoarthritis (OA) was initially recognized in 1941 by Stecher, who showed that Heberden’s nodes of the fingers were more common in sisters of affected subjects than in the general population (1). In 1963, Kellgren et al (2), in a study of subjects derived from an outpatient clinic, reported that first-degree relatives of subjects with generalized radiologic OA (ROA) were twice as likely to have ROA than was expected in the general population. In 1996, Spector et al (3) measured ROA in the hands and knees of female twins and suggested that genetic factors might explain up to 65% of the variability in ROA of the hand and knee. This familial aggregation of hand and knee ROA was confirmed recently in 2 population-based studies (4,5). Furthermore, Felson et al (4), in a segregation analysis, found evidence of effects of a major recessive gene with a residual multifactorial component.

With the exception of the study by Kellgren et al (2), previous studies concerning the role of genetic factors in the occurrence of ROA were limited to OA of the hands and knees (3–5). The contribution of genetic factors to other common forms of OA, including hip
ROA and disc degeneration of the spine, has not been studied. Two studies addressed the role of body mass index in the familial aggregation of ROA (4,5), but none of the previous studies examined the role of bone mineral density. This is important, because bone mineral density, like body mass index, is a risk factor for OA and is strongly influenced by genetic factors (6,7).

We performed a population-based study on the contribution of genetic factors to the occurrence of ROA and disc degeneration in the general population. To quantify the occurrence of ROA and disc degeneration in the general population, we have drawn a random sample of 1,583 individuals ages 55–70 years from the Rotterdam Study. Radiographs of the peripheral joints—the knees, hips, and hands—and of the thoracolumbar spine were scored for ROA and disc degeneration, respectively, in all subjects.

To estimate the genetic component in the etiology of ROA and disc degeneration, we studied the siblings of a subsample of 250 probands (ages 55–65 years) with ROA and disc degeneration at least 2 joint sites. In this relatively young age category, genetic predisposition may play a more predominant role than in the elderly, in whom environmental factors and aging may be more important determinants. Probands were selected based on the abnormalities present on radiographs of the knees, hips, hands, and spine. Probands had to be affected at 2 or more of these 4 joint sites. In individuals who had hand ROA in combination with disc degeneration of the spine, both highly prevalent conditions that are likely to occur in combination by chance in high frequency, a proband had to also have Heberden’s nodes so that the number of siblings being studied would be reduced. This selection of probands was carried out in order to ascertain the group with the highest a priori probability of genetic factors playing a role in the occurrence of ROA.

A flow chart of the participation of probands and siblings is shown in Figure 1. Of the 221 probands that were willing to participate (response rate 88%), 24 had no siblings. The remaining 197 probands had a total of 708 siblings who had been born alive. Of these 708 siblings, 168 were deceased, 63 lived abroad, 66 could not be contacted, 23 were not able to participate because of a disease other than OA, and for 20 individuals the reason for not participating was unknown. From the 368 siblings who could be contacted, we were able to recruit 257 siblings (70%). These 257 siblings were derived from 118 probands and were examined at the research center. A majority (64%) of the 111 siblings who, upon request, refused to enter into the study indicated that they had no particular reason to do so.

Measurements. For all individuals, the following radiographs were obtained: weight-bearing anteroposterior pelvic radiographs with both feet in 10° of endorotation, weight-bearing knee radiographs with the patellae in central position, anteroposterior radiographs of the hands and wrists, and lateral radiographs of the spine (T4–S1).

The exact definition of OA remains a matter of debate,
but the use of radiologically determined changes is widely accepted in epidemiologic research concerning OA (9,10). We used the Kellgren/Lawrence grading system (11) for all joint sites, since it incorporates classic features of radiologic OA (osteophyte formation and joint space narrowing) and since, in our opinion, no convincing evidence has thus far been given that these features should be regarded as completely independent markers of disease. Thus, ROA was assessed by means of the Kellgren/Lawrence grading system (grades 0–4), using the figures and legends of the original atlas of standard radiographs.

Two independent readers (CB and HAV), who had no knowledge of the subject’s other data, scored all radiographs. After each set of about 150 radiographs, the scores of the 2 readers were evaluated in order to reduce bias related to intra- and interrater agreement. Whenever the scores varied by ≥2 points or when one reader scored a radiograph as 2 and the other scored it as 1, a consensus score was obtained. Full agreement between readers was achieved in 44% of cases for hand ROA, scored at 8 different sites, in 87% of cases for hip ROA, in 88% of cases for disc degeneration of the spine, and in 89% of cases for knee ROA. ROA of the knee was only assessed in the tibiofemoral joint. ROA of the hand was assessed in each interphalangeal (IP) and metacarpophalangeal (MCP) joint, the first carpometacarpal (CMC), the trapeziocapitate, the radionavicular, and distal radioulnar joints.

By definition, ROA of the spine is confined to the apophyseal joints, but these joints could not be assessed on the lateral radiographs of the spine that were available. Instead, we assessed disc degeneration of the spine, of which the genetic etiology may be associated with the occurrence of ROA in the peripheral joints (12). Disc degeneration was scored using the Kellgren/Lawrence scale, in which grade 0 or 1 denotes no or doubtful disc degeneration, grade 2 denotes vertebral osteophytosis only, and grades 3 and 4 indicate vertebral osteophytosis accompanied by moderate or severe disc space narrowing. Three levels of the spine were scored separately: the thoracic, lumbar, and lumbosacral spine.

The presence of Heberden’s nodes was determined by an examination of the hands, which was performed by trained investigators (CB and HAV) at the research center without knowledge of the radiographic findings. Heberden’s nodes were scored in both hands separately and were classified as absent or present. Bone mineral density was measured at the femoral neck by dual-energy x-ray absorptiometry as described previously (13). Weight and height were measured at the research center according to standardized procedures.

**Classification of ROA.** A total of 36 separate joints, grouped into 8 groups, in the hands were scored for ROA: the distal interphalangeal, the IP joint of the thumb, the proximal interphalangeal, the MCP, the first CMC, the trapeziocapitate, the radionavicular, and the distal radioulnar joints. This rendered 16 groups of joints (right and left hands separately). Together with the right and left knee and hip joints and the 3 levels in the spine, the total number of joint groups was 23. We constructed a sum score in order to summarize the presence of ROA in the peripheral joints and disc degeneration in the spine as a quantitative trait. Each of the 23 joint groups that had been scored contributed 1 point to the sum score if the Kellgren/Lawrence score was ≥2.

Each joint site (the knee, hip, hand, and spine) was also examined separately. In these analyses, the hands were regarded as 1 joint group, consisting of 36 individual joints and 16 groups of joints in both hands. Hand ROA was analyzed as a semicontinuous trait, with a trait score equaling the number of joint groups in the hands that had a Kellgren/Lawrence score ≥2. Knee and hip ROA were analyzed as dichotomous traits, with definite ROA defined as a Kellgren/Lawrence score ≥2 in the right or left corresponding joint. The spine was also regarded as 1 joint group, consisting of 3 different levels, the thoracic, lumbar, and lumbosacral spine. Definite disc degeneration was defined as a Kellgren/Lawrence score ≥2 in any of the 3 levels scored.

**Statistical analysis.** Demographic variables in the population and siblings were compared using Student’s t-test and chi-square test. Distributions of the sum score of ROA and disc degeneration were nonparametrically tested using the Mann-Whitney test.

Heritability is defined as the ratio of all genetic variance to the total variance, and it was estimated in 2 steps. First, the variance of ROA and disc degeneration within a sibling pair was compared with the variance between pairs of siblings. If a genetic effect is present, the variance within a sibling pair is expected to be lower than the variance between sibling pairs. Second, we used the data on the variances of ROA and disc degeneration in the random sample of 1,583 individuals to derive heritability estimates for the general population. Correspondingly, heritability estimates were calculated for body mass index and bone mineral density of the femoral neck. Although we cannot exclude a role of shared environmental factors early in life, the influence of shared environment on the occurrence of ROA during late middle age is expected to be limited, given that siblings lead separate lives. Furthermore, the correlation of OA in spouses has been found to be low (4), suggesting the absence of a strong environmental factor. At the individual level, adjustments were made for known genetic risk factors for OA that siblings may share, including age, sex, body mass index, and bone mineral density.

To calculate the heritability estimates, a random effects model, in which random effects represent genetic effects (14), was fitted using maximum likelihood estimation (15). A linear model was used for the normally distributed outcomes: the sum score of ROA and disc degeneration (log transformed), hand ROA (log transformed), body mass index, and bone mineral density of the femoral neck. A logistic model was used for the binary outcomes: knee ROA, hip ROA, and disc degeneration of the spine.

Heritability estimates are presented with 95% confidence intervals (95% CI). The heritability estimates for ROA and disc degeneration are applicable to the general population under the assumptions that the sample drawn from the Rotterdam Study is a random sample from the population, the genetic variance within a sibling pair is independent of ROA status, and the influence of shared environment on this late-onset disease is limited.

**RESULTS**

Characteristics of the 118 probands, their 257 siblings, and the random population-based sample of 1,583 individuals from which the probands were derived
are shown in Table 1. Four joint sites were affected in 5 probands, 3 joint sites in 47 probands, and a combination of 2 joint sites in 66 probands. Of the 76 probands with at least hand ROA and disc degeneration of the spine, the combination most frequently affected, 28 also had Heberden’s nodes.

Siblings were recruited ~4 years after the probands had been examined at the research center (see Table 1). The frequency of knee ROA in the siblings was similar to the frequency found in the total sample. The frequency of hip ROA in siblings was lower than would be expected based on the data from the total sample. Hand ROA and disc degeneration were significantly more frequent in siblings than in the total sample.

The distributions of the sum scores of ROA and disc degeneration, expressing the total number of joints affected, for probands, siblings, and the random sample derived from the Rotterdam Study are shown in Figure 2. As can be seen, the distribution for siblings was positioned between the distributions for the probands and the total sample. The median of the sum score in siblings was significantly higher than that in the random sample and was similar to that in probands.

The heritability estimate of the sum score of ROA and disc degeneration was 0.78 (95% CI 0.52–0.98), after adjustment for age, sex, body mass index, and bone mineral density (Table 2). This indicates that up to 78% of the variance in the sum score of ROA and disc degeneration was explained by genetic factors, independent of the influences of age, sex, body mass index, and bone mineral density.

For the individual joint sites, heritability estimates are given in Table 2. In these analyses, hand ROA was analyzed as a normally distributed trait, according to the number of joint groups affected in both hands (maximum 16). Knee and hip ROA and disc degeneration of the spine were analyzed as dichotomous traits. As shown in Table 2, disc degeneration had the highest heritability (0.75; 95% CI 0.30–1.00). Hand ROA was also statistically significantly correlated in siblings

![Figure 2. Distribution of the sum score of radiologic osteoarthritis and disc degeneration of the spine in probands, siblings, and the total population-based sample.](image-url)
Heritability estimates for ROA, disc degeneration, body mass index, and bone mineral density

<table>
<thead>
<tr>
<th></th>
<th>Heritability estimate (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>Sum score of ROA and disc degeneration</strong></td>
<td>0.78 (0.52–0.98)†</td>
</tr>
<tr>
<td><strong>Knee ROA</strong></td>
<td>0.07 (0.00–0.41) (NS)†</td>
</tr>
<tr>
<td><strong>Hand ROA</strong></td>
<td>0.56 (0.34–0.76)‡</td>
</tr>
<tr>
<td><strong>Disc degeneration of the spine</strong></td>
<td>0.75 (0.30–1.00)‡</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td>0.53 (0.34–0.75)‡</td>
</tr>
<tr>
<td><strong>Bone mineral density of the femoral neck</strong></td>
<td>0.52 (0.25–0.70)‡</td>
</tr>
</tbody>
</table>

* For hip radiologic osteoarthritis (ROA), no heritability estimate was calculated because the frequency of hip ROA in siblings was lower than that in the random general population. 95% CI = 95% confidence interval; NS = not significant.
† Adjusted for age, sex, body mass index, and bone mineral density.
‡ Adjusted for age and sex.

DISCUSSION

The present study suggests that genetic factors play a substantial role in the occurrence of radiologic OA in the general population. Siblings of subjects with ROA and disc degeneration at multiple joint sites had higher frequencies of hand ROA and disc degeneration. However, the frequencies of knee ROA and hip ROA were equal and lower, respectively, as compared with a random sample of individuals derived from the Rotterdam Study.

When considering the total number of joints affected at 4 separate sites, i.e., the knees, hips, hands, and spine, we found that up to 78% of the total variance of this sum score of ROA and disc degeneration was explained by genetic factors. In particular, hand ROA and disc degeneration of the spine showed a statistically significant aggregation in siblings. Interestingly, the genetic influence on ROA established here is independent of the well-known genetic influences present in body mass index and bone mineral density, which were also observed in this study. Since heritability estimates were calculated with the use of both the data from the sibling pairs and a random population-based sample from which the probands were selected, these estimates are applicable to the general population (15). Our data suggest the existence of a genetic susceptibility to generalized cartilage degeneration, independently of the genetic influences of body mass index and bone mineral density.

In Table 3, the findings of the present study are compared with the findings of the 3 previous studies on the heritability of OA, including a twin study and 2 population-based studies (3–5). For the sake of comparability, we also calculated sib–sib correlations (Table 3). Except for the 2-fold higher correlation of hand ROA between siblings in the study by Hirsch et al (5), the sib–sib correlations in all 4 studies were reasonably similar, despite between-study differences in type of study population and criteria for ROA.

Table 3. Comparison of sib–sib correlations between the present study and 3 previous studies (a twin study and 2 population-based studies)*

<table>
<thead>
<tr>
<th>Author, year (ref.)</th>
<th>Sib–sib correlation for hand ROA</th>
<th>Sib–sib correlation for knee ROA</th>
<th>Sib–sib correlation for hand and knee ROA</th>
<th>Definition of ROA (ref.)</th>
<th>Study population</th>
<th>Statistical adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spector et al, 1996 (3)</td>
<td>0.24†</td>
<td>0.31†</td>
<td>0.20†</td>
<td>Burnett et al (18)</td>
<td>Dizygotic twins</td>
<td>Age, weight</td>
</tr>
<tr>
<td>Felson et al, 1998 (4)</td>
<td>Not given</td>
<td>Not given</td>
<td>0.09§</td>
<td>K/L (11)</td>
<td>Random population</td>
<td>Age, sex, BMI, PAI, multiple comparisons</td>
</tr>
<tr>
<td>Hirsch et al, 1998 (5)</td>
<td>0.65‡</td>
<td>0.09§</td>
<td>0.23§</td>
<td>K/L (11)</td>
<td>Community volunteers</td>
<td>Age, sex, BMI</td>
</tr>
<tr>
<td>Present study</td>
<td>0.30‡</td>
<td>0.31‡</td>
<td>0.31‡</td>
<td>K/L (11)</td>
<td>Random population</td>
<td>Age, sex, BMI, BMD</td>
</tr>
</tbody>
</table>

* ROA = radiologic osteoarthritis; K/L = Kellgren/Lawrence; BMI = body mass index; PAI = physical activity index; BMD = bone mineral density.
† P value not given.
‡ P < 0.001.
§ Not significant.
The present study is the first to report an increased frequency of disc degeneration in siblings of probands with ROA and disc degeneration, which suggests a shared genetic etiology for ROA and disc degeneration in humans. Furthermore, the present study suggests a genetic predisposition for ROA and disc degeneration at multiple sites, as measured by the sum score. Although 2 earlier studies examined familial aggregation of ROA by summing the number of joints affected, this is the first study to include hip ROA and disc degeneration of the spine in the sum score (4,5).

Disc degeneration in addition to hand ROA showed the highest heritability estimates, whereas the evidence of familial aggregation was weakest for the weight-bearing joints (the knee and hip joints), as reported previously (2,3,5). For the knee joint, environmental factors, e.g., previous trauma, may play a major role in the development of ROA. Several studies of autosomal dominant hip ROA suggest a genetic defect underlying hip ROA due to dysplasia (16,17). Findings of the present study suggest that such major genes contribute little to hip ROA in the general population. It should be noted that the power of the present study was most likely lower for knee and hip ROA (dichotomous traits) than for hand ROA, disc degeneration of the spine, and the sum score of ROA and disc degeneration, which could be analyzed as quantitative traits.

There are several potential biases associated with our study. Selection bias might play a role when response rates were associated with ROA. Of the 368 siblings who were eligible for our study, 111 refused to participate. In most instances, there was no particular reason for not participating. Seven subjects indicated that they were known to have OA and did not participate for that reason. Although in general nonresponse has most likely been at random, disability in elderly subjects with hip OA may have led to an underestimate of the number of hip ROA cases in siblings. Lateral knee radiographs were not available, which means that no data could be presented on patellofemoral OA (18). Finally, heritability estimates were not calculated for men and women separately because of insufficient numbers of sibling pairs of the same sex.

A priori, it is unlikely that environmental factors shared by siblings early in life will influence the development of ROA and disc degeneration during late middle age sufficiently to account for the data found in the present study. Moreover, we adjusted for possible shared factors by siblings, such as age, sex, body mass index, and bone mineral density. This did not change the essential results of the analyses, and the evidence of familial aggregation of ROA and disc degeneration remained statistically significant. Furthermore, our results on hand ROA and, to a lesser extent, on knee ROA were comparable with the results of Spector et al (3) in their study of twins, in which adjustments were made for environmental factors shared by twins by comparing monozygotic and dizygotic twin pairs. This suggests that the influence of shared environment on the familial aggregation of ROA may be very limited, which was recently supported by rejection of an environmental model in a segregation analysis of knee and hand ROA (4).

In conclusion, the present study shows a strong genetic effect for ROA and disc degeneration at multiple sites. Up to 78% of the total variance in ROA and disc degeneration can be explained by genetic factors, independently of the ( genetic) influence of body mass index and bone mineral density. In particular, a strong familial aggregation was found for hand ROA and disc degeneration of the spine. We found no evidence of a statistically significant genetic effect on the occurrence of knee and hip ROA at the general population level. Previous findings suggest that there may be 2 possible genetic pathways: first, the existence of a common recessive allele (frequency 0.45) and second, a polygenic form of inheritance, perhaps in interaction with environmental factors (4). The 2 different mechanisms involved may explain the strong clustering of ROA in families. However, the genes underlying the familial aggregation of ROA in the population remain to be determined.

REFERENCES


