Genetic influences on osteoarthritis in women: a twin study

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Abstract

***Objectives*—To assess the relative contribution of genetic and environmental factors to common forms of osteoarthritis of the hands and knees.**

***Design*—Classic twin study with unselected twins who were screened radiologically for osteoarthritis.**

***Subjects*—130 identical and 120 non-identical female twins aged 48-70 recruited from a London based twin register and through a national media campaign.**

***Main outcome measures*—Similarity in identical compared with non-identical twin pairs for radiographic changes at the interphalangeal and first carpometacarpal joints of the hands and the tibiofemoral joint and patellofemoral joint of the knee expressed as intraclass correlations.**

***Results*—The intraclass correlations of radiographic osteophytes and narrowing at most sites and the presence of Heberden's nodes and knee pain were higher in the identical pairs. The intraclass correlation of the total radiographic osteoarthritis score in identical pairs (*r*MZ) was 0·64 (SE 0·05) compared with 0·38 (0·08) in non-identical pairs. The proportion of genetic variance of total osteoarthritis score (osteophytes and narrowing) with modelling techniques was estimated at 0·54 (95% confidence interval 0·43 to 0·65) and ranged from 0·39 to 0·65 for different sites and features ($P < 0·001$) after adjustment for age and weight.**

***Conclusions*—These results demonstrate for the first time a clear genetic effect for radiographic osteoarthritis of the hand and knee in women, with a genetic influence ranging from 39-65%, independent of known environmental or demographic confounders. The results of this study should lead to further work on isolating the gene or genes involved in the pathogenesis of this common disabling disease.**

Introduction

Osteoarthritis is the most common cause of musculoskeletal disability in most developed countries. The site that causes the greatest burden of disability in public health terms is the knee, which is estimated to result in pain and loss of function in 10% to 15% of men and women aged over 45 years.[1] The aetiology and pathogenesis of the condition, however, remain largely unknown. It is more common in women[2] and has been strongly associated with several environmental risk factors including obesity,[3-5] previous injury,[6,7] meniscectomy,[8] and other physical and metabolic factors.[9] Early studies by Stecher in 1941 showed that Heberden's nodes of the fingers were three times more common in the sisters of 64 affected subjects as in the general population.[10] Small family studies performed in the early 1960s suggested that first degree relatives of probands were twice as likely also to have radiographic generalised disease as population controls.[11] The only previous twin study, which was never published in full, showed an increased concordance in radiological osteoarthritis in 10 identical pairs at a number of joint sites.[12]

Recent work on rare forms of the disease has renewed interest in the genetics of osteoarthritis. Two reports on three unrelated families demonstrated coinheritance of primary generalised osteoarthritis with specific alleles of the gene for type II procollagen (COL2A1) on chromosome 12, the precursor of the major protein of cartilage.[13,14] This was associated with a single base mutation of this allele in affected members of several families, all with evidence of an associated chondrodysplasia.[15,16] There is currently little evidence that the common forms of osteoarthritis are due to collagen mutations, and previous studies are inadequate to assess the overall contribution of genetic factors to osteoarthritis in the population.

We used a classic twin study to investigate osteoarthritis by taking unselected twin pairs who were screened radiographically, which is the traditional method for defining the disease in population studies.[9]

Subjects and methods

SUBJECTS

The study population consisted of female twins aged 48-69 years selected from two sources of volunteers: a normal twin register held at the Institute of Psychiatry, London, and directly through an advertising campaign in the media. The articles concerned osteoporosis and did not mention arthritis or the hypothesis being tested. Approval was obtained from the hospital ethics committee and full informed written consent was obtained at the first visit. Zygosity was determined by a standard questionnaire[17] and by multiplex DNA fingerprinting with variable tandem repeats.

PROCEDURES

Each twin provided information on joint symptoms[18] and was examined for the presence of Heberden's nodes of the fingers.[19] Height and weight were measured. Radiographs of the hands were obtained with a standard posteroanterior view and of the knees with the following: a weight bearing anteroposterior view in full extension; a lateral view in 30° flexion; and a skyline view in 45° flexion with a perspex positioning wedge. All radiographs were independently assessed by two trained observers who were blind to the pairings, zygosity, and clinical findings, and in cases of disagreement a third adjudicator was used. The radiological features of osteoarthritis of the knee in both the tibiofemoral and patellofemoral joint as well as the distal interphalangeal, proximal interphalangeal, and first carpometacarpal joint of the thumb were graded on a four point scale (0-3) for osteophytes and joint space by using a radiological atlas.[20] The intraobserver and interobserver reproducibility of the observations was tested on a subgroup of 50 knees and hands with good results: a κ statistic of over 0·68 for all sites and features, comparable with other similar studies.[19]

STATISTICAL ANALYSIS

As monozygotic twins are completely concordant for genetic factors any intrapair variation is due to environmental factors. For dizygotic twins, who share on average half of their genes, any intrapair variation is due to both environmental and genetic factors. Thus a comparison between the similarity in monozygotic and dizygotic twins allows us to estimate the extent to which genetic factors determine variation in the radiographic measures of osteoarthritis.

The genetic effect was determined in two ways.

Firstly, in a dichotomous analysis, each pair was

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classified either as osteoarthritis present in both twins, in one, or in neither, classified by feature and by site separately; and an estimate of twin similarity, the intraclass correlation, was calculated for monozygotic and dizygotic pairs.[21] Adjustment for confounders was performed by using odds ratios and conditional logistic regression.

In the second analysis, a total osteoarthritis trait score was obtained by totalling the osteophyte and narrowing scores at each site. A total hand and knee score was obtained by weighting each of the five sites equally. Intraclass correlations were calculated by using path modelling methods with maximum likelihood estimates with twin analysis software.[22] The data were $\log_{10}(n+1)$ transformed before analysis and potential confounding variables dealt with by combining them with the osteoarthritis traits in multiple linear regression equations and subsequently entering the residuals into the analysis. An estimate of the genetic variance was calculated from the model that fitted the data (appendix). The means and incidences and the pairwise differences of the demographic variables and prevalence of joint disease in the monozygotic and dizygotic twins were compared by using the Student's t test and χ^2 test.

Results

A total of 307 twin pairs contacted our unit to inquire about participating in the study, 125 from the normal twin register and 182 from the media campaign. Of these, 255 pairs attended. Five pairs were excluded as one twin had a disabling disease: one for multiple sclerosis, three for recently diagnosed cancer, and one for morbid obesity. Table 1 gives the characteristics of the 130 monozygotic and 120 dizygotic pairs included in the study. There were no significant differences in age, weight, height, cigarette use, age at menopause, oestrogen use, knee pain, and current or past physical activity scores between the two groups. The characteristics of twins subgrouped on the basis of the method of recruitment did not show any significant differences in the above characteristics. As expected there were greater similarities between monozygotic pairs for height, weight, age at menopause, smoking, menopausal status, and use of oestrogen than for dizygotic twins. Complete sets of analysable radiographs were available for the hands of 126 monozygotic pairs and 116 dizygotic pairs and for the knees of 125 monozygotic and 116 dizygotic pairs. The prevalence of radiological disease at the different sites was also similar in the two twin groups. The prevalence of radiographic osteophytes of the knee found in the twins as a group was similar to a group of 717 women aged 50-67 from our Chingford general population survey.[18]

With osteoarthritis defined as a dichotomous variable, the similarity for disease defined by narrowing or osteophytes was higher at all hand and knee sites in monozygotic than in dizygotic twin pairs (with the exception of the proximal interphalangeal joint), although most differences were not significant (table 2). The similarity of clinically ascertained Heberden's nodes was also higher in monozygotic than dizygotic pairs as was the presence of knee pain. Adjustment for age and weight as confounders or use of analyses restricted to a subgroup of pairs concordant for smoking, use of hormone replacement therapy, and weight for twins from the normal twin register produced similar results. When osteoarthritis was defined as a semicontinuous trait the intraclass correlation for monozygotic twins significantly exceeded that of dizygotic twins for all the sites and combinations of features measured, the range of intraclass correlations for monozygotic twins being 0·45 to 0·70 compared with 0·25 to 0·38 for dizygotic twins (table 3). The corresponding estimates of the proportion due to genetic factors varied from 0·44 to 0·72 and 0·39 to 0·65 when adjusted for age and weight and were all significant ($P<0·001$). The number of women with

Table 1—*Characteristics of all the monozygotic and dizygotic twins examined in study as individuals. Figures are means (SD) unless stated otherwise*

Variable	Monozygotic (n=260)	Dizygotic (n=240)*
Age (years)	58·7 (5·3)	57·6 (5·7)
Weight (kg)	63·7 (9·8)	64·0 (9·5)
Height (cm)	161·8 (5·7)	162·0 (6·1)
Current total activity†	7·21 (1·98)	7·32 (1·72)
Age at menopause (years)	48·8 (5·6)	48·2 (6·3)
No (%) who had ever used oestrogen replacement therapy	106 (40·7)	99 (41·3)
No (%) who had ever smoked	111 (42·7)	113 (46·9)
No (%) who were postmenopausal	241 (92·7)	218 (90·7)
No (%) who had ever had knee pain (>15 days)	116 (44·6)	100 (41·7)

*Independent t test for continuous variables, χ^2 for discrete variables all variables, $P>0·05$.
†Total activity is composite score of total amount of walking (0–4) plus activity at work and home (0–4) plus sporting activity (0–4).

Table 2—*Incidence of osteoarthritis defined categorically and resulting intraclass correlations in monozygotic (rMZ) and dizygotic (rDZ) twins*

Joint site and disease classification	Monozygotic pairs (n=130)			Dizygotic pairs (n=120)			Intraclass correlation		P value*
	Both	One	Neither	Both	One	Neither	rMZ (SE)	rDZ (SE)	
Distal phalangeal:									
Osteophyte	51	29	50	42	30	48	0·55 (0·08)	0·50 (0·08)	0·305
Narrowing	8	18	104	4	24	92	0·39 (0·12)	0·13 (0·11)	0·056
Proximal interphalangeal:									
Osteophyte	13	33	84	12	28	80	0·28 (0·10)	0·31 (0·10)	0·601
First carpometacarpal:									
Osteophyte	41	24	65	19	48	53	0·62 (0·07)	0·13 (0·10)	<0·0001
Narrowing	26	22	82	8	33	79	0·58 (0·08)	0·15 (0·10)	0·0004
Tibiofemoral:									
Osteophyte	15	25	90	5	23	92	0·42 (0·10)	0·19 (0·11)	0·061
Narrowing	7	23	100	3	18	99	0·27 (0·11)	0·17 (0·12)	0·259
Patellofemoral:									
Osteophyte	25	33	72	12	35	73	0·41 (0·09)	0·21 (0·10)	0·060
Narrowing	6	17	107	6	21	93	0·34 (0·12)	0·26 (0·12)	0·325
Heberden's nodes:									
Clinical	45	33	52	31	45	44	0·49 (0·08)	0·24 (0·09)	0·017
Pain:									
Ever	32	52	46	23	54	43	0·19 (0·09)	0·07 (0·09)	0·177

*One sided P value H_0: rMZ > rDZ.

Table 3—*Intraclass correlation coefficients (SE) for monozygotic (n=130) and dizygotic (n=120) twin pairs and estimates of proportion of variance explained by additive genetic effects (95% confidence intervals) on basis of osteophyte and narrowing trait scores*

Site and feature	Monozygotic	Dizygotic	Proportion (95% confidence interval)
All sites osteophyte and narrowing	0·64 (0·05)	0·38 (0·08)	0·65 (0·56 to 0·74)
All sites osteophyte and narrowing (adjusted*)	0·56 (0·06)	0·20 (0·09)	0·54 (0·43 to 0·65)
All sites osteophyte	0·70 (0·04)	0·42 (0·08)	0·72 (0·64 to 0·79)
All sites osteophyte (adjusted*)	0·65 (0·05)	0·28 (0·08)	0·65 (0·56 to 0·74)
All sites narrowing	0·48 (0·07)	0·23 (0·09)	0·46 (0·33 to 0·58)
All sites narrowing (adjusted*)	0·42 (0·07)	0·17 (0·09)	0·41 (0·28 to 0·54)
Hand osteophyte and narrowing	0·65 (0·05)	0·37 (0·08)	0·65 (0·56 to 0·74)
Hand osteophyte and narrowing (adjusted*)	0·62 (0·05)	0·24 (0·09)	0·59 (0·49 to 0·70)
Knee osteophyte and narrowing	0·45 (0·07)	0·25 (0·09)	0·44 (0·31 to 0·56)
Knee osteophyte and narrowing (adjusted*)	0·42 (0·07)	0·17 (0·09)	0·39 (0·26 to 0·52)

*Adjusted for age and weight.

positive narrowing scores at the knee and hand alone was too small to interpret. Adjustment for the effect of additional potential confounders such as use of hormone replacement therapy, smoking, exercise, menopause, and height had little effect on the estimates.

Discussion

These data provide clear evidence of a genetic effect on osteoarthritis in women. The correlations of disease trait and disease status were consistently higher in identical compared with non-identical twins. Thus 39% to 65% of the variance of osteoarthritis in the hand and knee can be attributed to genetic factors. This genetic effect was consistent whichever radiographic diagnosis of osteoarthritis was used or whether it was defined clinically as knee pain or Heberden's nodes.

DIAGNOSIS OF OSTEOARTHRITIS

Case definition in osteoarthritis research remains problematic; it depends on the groups being studied and the purpose of identifying individual patients. There is a general consensus that radiological changes are the preferred method for epidemiological study[9 23 24] on the basis of cross sectional[3-8 25] and prospective[26 27] correlations between severity of *x* ray changes with the presence of pain and loss of function. Osteophytes and narrowing of joint space are the classic features of osteoarthritis, and both are probably independent markers of disease.[28 29] The estimates of genetic influences, however, remained remarkably robust to changes in definition.

POTENTIAL BIASES

There are several potential problems associated with twin studies; the primary source of bias in disease studies is through ascertainment of affected cases with an overrepresentation of monozygotic and concordant twins and hence misleadingly high rates of concordance.[30] We avoided many of the potential problems of case ascertainment bias by using population based twins; with similar results when the media twins were excluded. A recent study of rheumatoid arthritis in twins in the United Kingdom found no evidence of selection bias with various methods of recruitment, including media advertising and clinical case referrals.[31] The other important considerations in twin analyses is the assumptions underlying the analyses, which include, firstly, that the variances of the trait are similar in monozygotic and dizygotic twins (in this case the radiographic scores which were similar in all analyses), and, secondly, that shared environment is similar in monozygotic and dizygotic twins.[32] We have shown that small differences did exist, such as weight, although adjustment for this or others did not affect our results. A further possible confounding factor in twin studies can arise from differences in early fetal environment. Most monozygotic twins share the same placenta and chorion, whereas dizygotic pairs do not.[33] This could affect research in which early fetal environment is believed to be important, such as in cardiovascular disease or diabetes, but to date there is no evidence of a similar influence in osteoarthritis. The final assumption is that there are no major gene interactions which are indicated by lower than expected concordance rates in dizygotic pairs and heritability estimates above one. There was little consistent evidence of this, but estimates of the extent of the genetic effect should always be treated with caution.

POSSIBLE MECHANISMS

Our data suggest a genetic predisposition for osteoarthritis at all sites. These findings, in addition to current views that environmental risk factors act differently at different sites, such as the effects of obesity and occupation, point towards pronounced heterogeneity in environmental and genetic interactions. The strong genetic influence does not make osteoarthritis "inevitable." There are probably important genetic-environmental interactions such that changes in lifestyle in predisposed people may have a strong effect. The nature of the genetic effect is speculative and may entail either a structural defect (for instance, collagen) or alterations in cartilage or bone metabolism. It is therefore possible that the turnover or repair of cartilage and bone is under genetic control with different thresholds and responses in genetically distinct subjects.

In conclusion, we have shown a clear genetic effect for osteoarthritis of the hand and knee in women, with up to 65% of the variance in twins being explained by genetic factors. This should stimulate further work in identifying the principal genes concerned and exploiting this knowledge.

Key messages

- Osteoarthritis of the knee causes pain and disability in more than 2 million adults in the United Kingdom alone
- Although environmental factors have traditionally been thought to be the main influences, there are few data to support this
- Between 39% and 65% of osteoarthritis in the general population can be attributed to genetic factors
- Identification of the genes concerned could have a large impact on the disease in terms of prevention and new therapeutic approaches

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Conflict of interest: None.

Appendix

The aim of the analysis was to partition the observed features of osteoarthritis into genetic and environmental

components by comparing the similarity within each pair between zygosities. Intraclass correlation coefficients (r) were used as a measure of similarity. One way analysis of variance was used to partition the total variation of osteoarthritis into between pair (B) and within pair (W) variations. The estimate of r is given by the difference between B and W over their sum—that is, $(B-W)/(B+W)$ where the approximate $SE=\sqrt{(1-r)^2(1+r)^2/(n-1)}$ (where r=intraclass correlation, n=number of pairs). A path maximum likelihood (PATH-ML) method was used to estimate the genetic effect. The variances-covariances are expressed as a function of four main effects: additive genetic (A), dominant genetic (D), common environment (C), and specific environment for an individual, including measurement error (E). There was no evidence of a dominant effect and the models tested were, firstly, $y_{ij}=\mu+A_{ij}+C_{ij}+E_{ij}$, secondly, $y_{ij}=\mu+A_{ij}+E_{ij}$, thirdly, $y_{ij}=\mu+C_{ij}+E_{ij}$ (i=family cluster; j=individual within family). There was no significant improvement of the first over the second, suggesting no significant effect of C. The AE model was therefore tested against E to obtain a level of significance with the goodness of fit likelihood ratio statistic.

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Commentary: Genes for osteoarthritis: interpreting twin data

John Hopper

> "This is indeed a mystery," I remarked. "What do you imagine that it means?"
>
> "I have no data yet. It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts." [1]

Anyone can theorise that genes have a role in determining who gets which diseases and at what stage of life. Anyone can imagine that the world is round not flat. The key element, however, is to show that one's theory is believable by gathering and analysing data, and more data, using designs that ever more critically assess the hypotheses at stake. Columbus was not alone in his anti-flat earth imaginings, but he is famous because he collected critical data (even though he may not have interpreted all of it correctly, given the concept American Indians).

The classic twin method is a clever means of trying to untangle the role of genes from that of shared non-genetic influences on individual characteristics. The similarity of monozygotic (one egg) twin pairs, who are genetically identical, is compared with that of dizygotic (two eggs) twin pairs, who are on average genetically half identical. Given that sampling issues are adequately dealt with,[2] the finding that monozygotic pairs are more similar than dizygotic pairs is consistent with the genetic hypothesis but certainly does not prove it.

If the extent to which twin pairs share the non-genetic influences for that characteristic is truly no greater in monozygotic pairs, however, the genetic hypothesis is substantiated. In applying the classic twin method this is almost always theorised to be the case. The catch, of course, is that it in practice is very difficult to test the veracity of this condition. There is substantial evidence that living together contributes to humans being more similar in lifestyle and psychological, physiological, and other characteristics.[2,3] Dependent on the characteristic in question, this cohabitation effect may abate quickly or slowly as pairs begin to live apart, and may be greater for monozygotic twin pairs.[3-5]

When the classic twin method is applied, therefore, failure to consider zygosity differences in the effects of cohabitation may lead at best to overestimates of and at worst to invalid conclusions about a genetic role.

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