

Osteoarthritis and Cartilage



International
Cartilage
Repair
Society



Genetic influence on the progression of radiographic knee osteoarthritis: a longitudinal twin study¹

G. Zhai Ph.D.^{†*}, D. J. Hart Ph.D.[†], B. S. Kato Ph.D.[†], A. MacGregor M.D.^{†‡} and T. D. Spector M.D.[†]

[†] Twin Research & Genetic Epidemiology Unit, St Thomas' Hospital, London, UK

[‡] School of Medicine, University of East Anglia, Norwich, UK

Summary

Objective: Genetic influences on rates of osteoarthritis (OA) progression are unknown. Our aim was to estimate the heritability of progression of radiographic knee OA using a longitudinal twin study.

Methods: Unselected monozygotic (MZ) and dizygotic (DZ) twin pairs from the TwinsUK registry were utilized. Anteroposterior radiographs were performed on both knees at baseline and follow-up using the same protocol. Radiographic features of knee OA including osteophyte and joint space narrowing (JSN) were assessed on a four-point scale using a standard atlas. Progression of knee osteophyte and JSN was defined as the difference in the corresponding score between follow-up and baseline ≥ 1 . Liability threshold modelling using logistic regression was utilized for heritability estimation.

Results: A total of 114 MZ pairs and 195 DZ pairs were studied. The average follow-up time was 7.2 years. Medial progression of osteophyte and JSN was more common than lateral progression. Prevalence of progression was generally higher in the MZs than the DZs. Similarly, concordances and tetrachoric correlations for both osteophyte and JSN were higher in the MZs than the DZs although only significant for overall and medial JSN and osteophyte. The heritability estimates were 69% [95% confidence interval (CI) 42–97%] and 80% (95% CI 50–100%) for medial osteophyte and JSN, respectively. The estimates were reduced by 7–15% after adjustment for age, body mass index (BMI), and the severity of osteophyte/JSN at baseline.

Conclusion: Our data documented a substantial genetic influence on the progression of knee OA – as seen in the medial compartment, providing a solid basis to search for genes involved in this highly relevant clinical trait.

© 2006 OsteoArthritis Research Society International. Published by Elsevier Ltd. All rights reserved.

Key words: Genetics, Knee osteoarthritis, Progression.

Introduction

Osteoarthritis (OA) is the most common form of arthritis and a leading cause of musculoskeletal disability in most developed countries¹. The knee is one of the most frequently affected joints with a prevalence of 30% in people older than 65 years² and high resultant disability³. Despite this, its aetiology and pathogenesis remain poorly understood. Risk factors including obesity, previous knee injury, high bone mineral density (BMD) have been associated with knee OA. These factors may operate differently at different stages of the disease. Some factors such as obesity, previous knee injury, and regular physical activity have been linked to incidence, yet in the same populations appear unrelated to the risk of progression⁴. While high BMD is associated with incidence of knee OA, low BMD is associated with progression of the disease⁵. Indeed, after the disease is established, some cases remain stable for a long period while others progress rapidly. These suggest that there may

be different risk factors for the progression of the disease. It is often assumed that genetic influences are similar for prevalent and progressive disease traits – yet in hand OA, while the prevalent hand OA is highly heritable⁶, a longitudinal family study reported that there was no genetic influence on progression of the hand OA⁷.

Using a classic twin study, we previously reported a significant but moderate genetic component to prevalent knee OA⁶. However, it is unknown whether this genetic influence also operates on the progression of the disease. The aim of this study, therefore, was to estimate the heritability of the progression of the radiographic knee OA in a longitudinal twin study.

Subjects and methods

STUDY SUBJECTS

Based on the power calculation, a matched and balanced sample of female twins aged 40 years or over with knee X-ray data available at baseline was derived from the Twins UK Adult Twin Registry, a group ascertained to study the heritability and genetics of age-related diseases. These unselected twins were recruited from the general population through national media campaigns in the UK and shown to be comparable to age-matched population singletons in

¹ Sources of Support: Arthritis Research Campaign.

*Address correspondence and reprint requests to: Guangju Zhai, Ph.D., Twin Research & Genetic Epidemiology Unit, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK. Tel: 44-20-7188-6738; Fax: 44-20-7188-6761; E-mail: guangju.zhai@kcl.ac.uk

Received 7 July 2006; revision accepted 2 September 2006.

terms of disease-related and lifestyle characteristics⁸. All subjects were Caucasian. The study was approved by St Thomas' Hospital Research Ethics Committee and all twins provided informed written consent.

RADIOGRAPHS

Anteroposterior extended-view weight-bearing radiographs of both knees were obtained at baseline and follow-up using the same protocol. Views were standardized with the backs of the knees in contact with the cassette, the patella centralized over the lower end of the femur, and the beam centered 2.5 cm below the apex of the patella, with a tube-to-film distance of 100 cm. All radiographs were assessed by one single experienced observer (DH) who was blind to the pairings, zygosity, and clinical findings. Using a standard atlas, radiographic features of osteophyte and joint space narrowing (JSN) were assessed on a four-point scale for increasing severity at lateral and medial compartments of both knees⁶. The intraobserver and interobserver reproducibility of the observations was tested on a subgroup of 50 knees with good results: a (kappa) statistic of over 0.68 for all sites and features.

The difference in the corresponding scores of osteophyte and JSN at each compartment between follow-up and baseline was calculated and the progression of osteophyte and JSN was defined as the difference ≥ 1 . This definition has been used by others⁹. Overall progression of osteophyte and JSN was then defined as at least one of four compartments (e.g., left and right knee lateral and medial compartments) having progressed.

STATISTICS

Basic characteristics of study subjects were compared between monozygotic (MZs) and dizygotic (DZs) using *t* test or Chi-squared test wherever appropriate. Casewise concordance, an estimator of the probability that one twin is affected given that the other is affected, for the MZs and the DZs was calculated by likelihood-based approach¹⁰. Under the assumption that there is a normally distributed liability and that individuals with liability above a certain threshold develop the disease, tetrachoric correlation coefficients, a measure of association (strength) of the relationship between two dichotomous variables, were also calculated and compared between the MZs and the DZs. A significantly higher correlation in the MZs than in the DZs would indicate a genetic influence on the trait. Liability threshold modelling, which assumes underlying continuous liability to a dichotomous trait, using logistic regression¹¹ was then used and the heritability was defined as the proportion of total variance due to additive genetic effects, assuming that the phenotypic variance is due to additive genetic factors (*A*), shared environmental factors (*C*), and non-shared environmental factors (*E*). We chose this method because it allows us easily to adjust for covariates such as age and body mass index (BMI). A *P* value less than 0.05 (two-tailed) or a 95% confidence interval (CI) not including the null point was considered statistically significant. All the analysis was performed in STATA (StatCorp LP, College Station, TX, USA).

Results

A total of 228 MZ twins (114 pairs) and 390 DZ twins (195 pairs) were studied. The average follow-up time was 7.2 years (range 5–10 years). The basic characteristics of the

study participants are presented in Table I. The MZs were on average 4 years older than the DZs. The DZs were taller and heavier than the MZs group but there was no significant difference in BMI. The prevalence of osteophyte and JSN at both baseline and follow-up was slightly higher in the MZs than in the DZs except for baseline osteophyte although differences were not statistically significant.

Table II presents the results of the prevalence, casewise concordance, and tetrachoric correlation coefficients of the progression of osteophyte and JSN between the MZs and DZs. Overall and medial progression of osteophyte and JSN was more common than lateral progression as expected. Prevalence of progression was higher in the MZs than the DZs except for lateral JSN. Similarly, the concordances for both osteophyte and JSN were higher in the MZ than the DZ group although only significant for overall JSN and medial osteophyte. Tetrachoric correlation was significantly higher in the MZs than the DZs for overall and medial osteophyte and JSN, but not for lateral osteophyte. There were not enough cases to perform meaningful analyses for lateral JSN.

By using the liability threshold model, the best fitting model included additive genetic factors and non-shared environmental factors and the heritability estimates were significantly higher for both medial osteophyte and JSN (Table III). After adjustment for age, BMI, and the severity of osteophyte/JSN at baseline, the heritability estimates were reduced by 7–15%. The estimates were similar if adjusted for height and weight instead of BMI. The prevalence of progression of lateral JSN was low and small numbers of cases prevented us from obtaining a meaningful estimate of heritability while the similar tetrachoric correlation in lateral osteophyte progression between the MZ and the DZ tentatively suggested no clear genetic influence.

Discussion

These data provide clear evidence that progression of radiographic knee OA as seen most commonly in the medial compartment has a significant genetic component. The correlation of medial JSN and osteophyte was significantly higher in MZ than DZ twins. The heritability estimate ranged from 48% to 71% independent of age and BMI.

Genetic influence on prevalent knee OA has been reported^{6,12,13} although not replicated in all studies^{14,15}. In a previous cross-sectional twin study⁶, we documented

Table I
Characteristics of the study sample*

	MZ (n = 228)	DZ (n = 390)	<i>P</i> value
Follow-up time	7.1 (0.24)	7.28(0.29)	<0.0001
Age at follow-up (years)	58.4 (0.49)	54.5 (0.36)	<0.0001
Height at baseline	1.61 (0.004)	1.62 (0.003)	0.01
Weight at baseline	64.5 (0.70)	66.3 (0.59)	0.05
BMI at baseline	24.9 (0.25)	25.2 (0.22)	0.32
Prevalence of JSN at baseline	19%	14%	0.11
Prevalence of osteophyte at baseline	20%	21%	0.76
Prevalence of JSN at follow-up	27%	24%	0.42
Prevalence of osteophyte at follow-up	37%	33%	0.33

**t* Test or Chi-squared test was used wherever appropriate.

Table II
Analysis of the progression of knee OA traits*

	MZ			DZ		
	Prevalence (%)	Ccase (%)	Tetrachoric correlation	Prevalence (%)	Ccase (%)	Tetrachoric correlation
JSN	20.2	57	0.745	18.0	34†	0.424‡
Medial JSN	17.6	53	0.728	15.3	41	0.590†
Lateral JSN	2.3	50	0.95	2.9	—	—
Osteophyte	34.7	58	0.556	27.4	45	0.424†
Medial osteophyte	25.7	58	0.686	19.7	35†	0.380‡
Lateral osteophyte	19.4	30	0.363	12.7	25	0.387

*Progression was dichotomously defined as the difference score ≥ 1 . Prevalence was defined as the percentage of subjects who had progression of knee OA traits. Ccase: casewise concordance. † $P \leq 0.05$; ‡ $P < 0.0001$.

a significant but moderate heritability estimate for radiographic knee OA with a heritability of 39%. This follow-up study is consistent with our previous results⁶, adding further weight to the finding that prevalent knee OA as well as progression have a genetic component. Substantial higher heritability estimates in this longitudinal study compared with the cross-sectional results⁶ suggest that the patterns of genetic control to the knee OA may vary over a given time course. Some genetic factors may only be responsible for the initial development of the disease while others may switch on for the disease progression. Cross-sectional studies would not be able to capture all the information about the disease process. Longitudinal studies include more information and thus provide better estimates. However, a longitudinal family study found no genetic influence on the progression of hand OA⁷. The discrepancy with the current study suggests that progression may be joint specific, but the family study⁷ may possibly be confounded by age differences, cohort effects, and the difficulty separating shared environmental and genetic factors.

In contrast to our previous study⁶, we only found that changes in the medial compartment were clearly heritable. This is surprising but consistent with a recent magnetic resonance imaging (MRI)-based study¹⁶ in which a stronger genetic influence was also found for medial cartilage loss. The reason for this site specific influence is unclear. It may reflect greater random variability and error in the measurement of the lateral compartment but may relate to why OA targets the medial compartment more commonly than the lateral compartment¹⁷. Indeed, lateral progression in the current study was far less common, particularly for lateral JSN, as has been found in recent trials¹⁸.

Numerous genome-wide linkage scans of OA have been conducted and several regions have been identified as harbouring susceptibility genes for OA, although most of them

focused on hand and hip joints¹⁹. Association studies of candidate genes have reported several susceptibility genes for knee OA including COL1A1 ($\alpha 1$ chain type I collagen), COL2A1 ($\alpha 1$ chain type II collagen), VDR (vitamin D receptor), and IGF-I (insulin-like growth factor-1)¹⁶. We recently reported that BMP2 (bone morphogenetic protein 2), CD36 (collagen type I receptor, thrombospondin receptor), COX2 (prostaglandin-endoperoxide synthase 2), and NCOR2 (nuclear receptor corepressor 2) were associated with prevalent knee OA while CILP (cartilage intermediate-layer protein), OPG (osteoprotegerin), and TNA (tetranectin) were associated with the progression¹⁷. Only one gene (e.g., ADAM12 – a disintegrin and metalloproteinase domain 12) was found to be associated with both prevalent and progression of knee OA. Lack of overlap of susceptibility genes between prevalent and progression of knee OA could arise for a variety of reasons, but may suggest a different set of genes operating on the progression of the disease.

Despite the significant findings, there are some caveats in the current study. Firstly, a traditional criticism of twin studies is that they may theoretically overestimate the heritability due to a failure of the assumption of similar shared environments between MZ and DZ twins. However, there is no evidence that any chronic disease heritability including OA is influenced to any degree by minor degrees of extra environmental sharing – even if it exists – which is unproven. A recent longitudinal sibpair study which is less sensitive to shared environments reported similar results with a heritability of 63% for medial cartilage loss measured by MRI¹⁶, suggesting that the estimates in the current study are reliable. Secondly, the measurement error in the assessment of JSN and osteophyte may bias the estimates. However, this bias would lead to an underestimate of heritability and our reproducibility was high, suggesting this is not of major concern. Lastly, the prevalence of knee OA differs between males and females. The sample in the current study composed of only females, and consequently the results cannot be generalized to males.

In conclusion, our data document a substantial genetic influence on the progression of knee OA, providing a good rationale for discovery of genes (and therefore novel mechanisms) influencing the rate of progression and severity of knee OA which could be of major therapeutic potential.

Acknowledgement

We would like to acknowledge the Arthritis Research Campaign for their support with this study and all the twins participating in the study. We thank Dr Toby Andrew for his

Table III
 H^2 for various traits using liability threshold models*

	Univariable analysis		Multivariable analysis	
	H^2	95% CI	H^2	95% CI
JSN	0.741	0.46–1.00	0.627	0.33–0.92
Medial JSN	0.798	0.50–1.00	0.713	0.41–1.00
Lateral JSN	—	—	—	—
Osteophyte	0.621	0.37–0.87	0.476	0.21–0.74
Medial osteophyte	0.694	0.42–0.97	0.620	0.34–0.90
Lateral osteophyte	0.328	0.02–0.63	0.180	–0.15–0.51

* H^2 : heritability estimates. Multivariable analysis adjusted for age, BMI, and the severity of osteophyte/JSN at baseline. Age and BMI accounted for 5% and 11% of the trait variance, respectively.

help of implementing liability logistic regression in the STATA. We also thank Professor Harold Sneider, Professor Gregory Livshits, and Dr Dongliang Ke for helpful discussion.

References

1. Reginster JY. The prevalence and burden of arthritis. *Rheumatology (Oxford)* 2002;41(Suppl 1):3–6.
2. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum* 1987;30(8):914–8.
3. Spector TD, Hart DJ. How serious is knee osteoarthritis? *Ann Rheum Dis* 1992;51(10):1105–6.
4. McAlindon TE, Wilson PW, Aliabadi P, Weissman B, Felson DT. Level of physical activity and the risk of radiographic and symptomatic knee osteoarthritis in the elderly: the Framingham study. *Am J Med* 1999;106(2):151–7.
5. Hart DJ, Cronin C, Daniels M, Worthy T, Doyle DV, Spector TD. The relationship of bone density and fracture to incident and progressive radiographic osteoarthritis of the knee: the Chingford Study. *Arthritis Rheum* 2002;46(1):92–9.
6. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in women: a twin study. *BMJ* 1996;312(7036):940–3.
7. Kalichman L, Kobylansky E, Seibel MJ, Livshits G. Repeated measurement study of hand osteoarthritis in an apparently healthy Caucasian population. *Am J Hum Biol* 2005;17(5):611–21.
8. Andrew T, Hart DJ, Snieder H, de LM, Spector TD, MacGregor AJ. Are twins and singletons comparable? A study of disease-related and lifestyle characteristics in adult women. *Twin Res* 2001;4(6):464–77.
9. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. *JAMA* 2001;286(2):188–95.
10. Witte JS, Carlin JB, Hopper JL. Likelihood-based approach to estimating twin concordance for dichotomous traits. *Genet Epidemiol* 1999;16(3):290–304.
11. Sham PC, Walters EE, Neale MC, Heath AC, MacLean CJ, Kendler KS. Logistic regression analysis of twin data: estimation of parameters of the multifactorial liability-threshold model. *Behav Genet* 1994;24(3):229–38.
12. Neame RL, Muir K, Doherty S, Doherty M. Genetic risk of knee osteoarthritis: a sibling study. *Ann Rheum Dis* 2004;63(9):1022–7.
13. Chitnavis J, Sinsheimer JS, Clipsham K, Loughlin J, Sykes B, Burge PD, *et al.* Genetic influences in end-stage osteoarthritis. Sibling risks of hip and knee replacement for idiopathic osteoarthritis. *J Bone Joint Surg Br* 1997;79(4):660–4.
14. Riyazi N, Meulenbelt I, Kroon HM, Runday KH, Hellio le Graverand MP, Rosendaal FR, *et al.* Evidence for familial aggregation of hand, hip, and spine but not knee osteoarthritis in siblings with multiple joint involvement: the GARP study. *Ann Rheum Dis* 2005;64(3):438–43.
15. Bijkerk C, Houwing-Duistermaat JJ, Valkenburg HA, Meulenbelt I, Hofman A, Breedveld FC, *et al.* Heritabilities of radiologic osteoarthritis in peripheral joints and of disc degeneration of the spine. *Arthritis Rheum* 1999;42(8):1729–35.
16. Zhai G, Ding C, Stankovich J, Cicuttini F, Jones G. The genetic contribution to longitudinal changes in knee structure and muscle strength: a sibpair study. *Arthritis Rheum* 2005;52(9):2830–4.
17. Neame R, Zhang W, Deighton C, Doherty M, Doherty S, Lanyon P, *et al.* Distribution of radiographic osteoarthritis between the right and left hands, hips, and knees. *Arthritis Rheum* 2004;50(5):1487–94.
18. Brandt KD, Mazzuca SA. Experience with a placebo-controlled randomized clinical trial of a disease-modifying drug for osteoarthritis: the doxycycline trial. *Rheum Dis Clin North Am* 2006;32(1):217–34, xi–xii.
19. Loughlin J. The genetic epidemiology of human primary osteoarthritis: current status. *Expert Rev Mol Med* 2005;7(9):1–12.