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Joint-specific twin and familial aggregation of recalled physician diagnosed osteoarthritis

Urho M Kujala [1], Jenni Leppävuori[2], Jaakko Kaprio[3], Jaakko Kinnunen[4], Leena Peltonen[2] and Markku Koskenvuo[5]

[1]Unit for Sports and Exercise Medicine, Institute of Biomedicine, University of Helsinki
[2]Department of Human Molecular Genetics, National Public Health Institute, Helsinki
[3]Department of Public Health, University of Helsinki
[4]Department of Diagnostic Radiology, Helsinki University Hospital, Helsinki
[5]Department of Public Health, University of Turku, Turku, Finland

In our three-stage questionnaire study we investigated patterns of twin and familial aggregation of osteoarthritis (OA) for commonly affected joints. The baseline questionnaire study of the Finnish Twin Cohort was performed in 1975. In 1990, 4095 twin pairs of the same gender born 1930–1957 responded to a questionnaire and reported whether they had OA diagnosed by a physician. In 1996 both twins of 266 pairs of which at least one had reported OA in 1990 responded to a detailed questionnaire on joint-specific OA, including family history of OA. In male pairs shared (non-genetic) familial effects accounted for 37% of the total variance in liability to OA and unshared environmental effects for 63%. In female pairs additive gene effects explained 44% of the variance in liability to OA, and unshared environmental effects for 36%. Familial aggregation of finger and knee OA was clearly higher than that of hip OA. Twin-pair discordance for OA was, to some extent, associated with body-mass index, occupational loading and trauma. Our results indicate that genetic effects may be modulated by sex or by environmental factors distributed differently between men and women. Based on our joint-specific data finger and knee joints are the most optimal targets for studies of genetic factors predisposing to the development of OA.

Keywords: osteoarthritis, epidemiology, genetics, twin research

Introduction

The suspected risk factors for osteoarthritis (OA) include genetic predisposition,[1–3] obesity,[4,5] previous injuries,[5–7] and various physical loading conditions.[4,8–10]

Some types of work-related loading, such as handling of heavy material and work involving kneeling, have been associated with a higher incidence of OA of lower-limb joints.[4,7,8] In particular, meniscal and ligamentous knee injuries predispose to knee OA.[7] Heliövaara et al[11] reported that in terms of the population attributable fraction, prior trauma, physical stress and body mass explained 59% of the prevalence of hip OA. However, studies investigating the relationship between loading patterns and the pathogenesis of OA have in general been able to explain only less than one half of the variation in the occurrence of OA. Hand joints are not weight-bearing, and unilateral hand OA does not correlate with hand laterality[12] ruling out at least a major influence of physical loading in the etiology of hand OA, even though manual work may be associated with the occurrence of hand OA. Even though the role of various types of loading in the development of OA is still incompletely understood, genetic factors are of substantial interest. Familial liability to OA may be mediated by genes having a direct effect on the biology of the cartilage and other tissue components of joints, but also by other factors that may accumulate into families, such as obesity and occupational class.

A recent report by Spector and colleagues[13] describes the genetic influences on OA in monozygotic and dizygotic female twins and concludes that the results show a distinct genetic effect of the hand and knee OA in women (ranging from 39% to 65%), independent of known environmental or demographic confounders. These figures can be considered as an upper bound of the genetic influence. Previous studies have shown high familial aggregation of Heberden's nodes.[14,15] The presence of Heberden's nodes was shown to be strongly associated with polyarticular primary OA.[16] Based on earlier studies it also seems that familial aggregation of hand and knee OA is higher than that of hip OA.[17,18]

Correspondence: Dr UM Kujala, Unit for Sports and Exercise Medicine, Mannerheimintie 17 (Töölö Sports Hall), FIN-00250 Helsinki, Finland. Tel: +358 9 4342100; Fax: +358 9 90809; E-mail: urho.kujala@helsinki.fi
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OA is a component of many osteochondrodysplastic syndromes which follow Mendelian modes of inheritance. Mutations have been identified in genes encoding extracellular matrix proteins of cartilage such as type II collagen[3] and other cartilage collagens including COL11A2[19] and COL9A2.[20] Other loci involved in syndromic OA comprise cartilage oligomeric matrix protein,[21] a sulphate transport protein,[22] and FGFR3.[23] However, mutations in these genes are unlikely to be primary causes of OA without syndromic features. The etiology of the common form of primary OA seems to be multifactorial, different defects in multiple genes together with environmental factors causing the disease. Sib pair analysis and linkage studies in families with nonsyndromic OA should expose new loci predisposing to this common complex trait.

Exact knowledge on the joint-specific familial aggregation of OA would benefit the planning of optimal study designs to define the genetic factors predisposing to the development of OA. To this aim we investigate the twin and familial aggregation of OA in overall and the differences in the aggregation by joint.

Materials and methods

The Finnish Twin Cohort includes all twin pairs of the same gender born before 1958 with both co-twins alive in 1967,[24] who were selected from the Central Population Registry of Finland in 1974. A general health questionnaire was mailed to this cohort in 1975. In the 1975 questionnaire the subjects reported their weight and height based on which we calculated body-mass index (kg/m^2). The questionnaire also included a question on the occupational loading of the subject's current or latest job with four alternatives:

(i) mainly sedentary work,

(ii) job includes mainly standing and walking without heavy physical loading,

(iii) in addition to standing and walking the job includes lifting and carrying, and

(iv) heavy manual work.

A first follow-up general health questionnaire in 1981 included the same items.

In 1990 a second follow-up general health questionnaire was mailed to twin pairs with both co-twins known to be alive and resident in Finland in 1987, who were born between 1930 and 1957 (aged 33 to 60 years) (n = 17 876 twin individuals, 8938 pairs). In October 1990, 16 179 twin individuals could be contacted and 12 504 returned the questionnaire (response rate 77.3%). The questionnaire consisted of 103 multiple-choice questions, including the body-mass index and occupational loading items as in 1975. Both members of 4095 twin pairs (1757 men pairs [577 MZ and 1180 DZ] and 2338 women pairs [836 MZ and 1502 DZ]) responded to the questionnaire (Table 1) and

Table 1 Reports of physician-diagnosed osteoarthritis (OA) by age-group and zygosity in the 4097 twin-pairs of whom both answered the 1990 questionnaire and aged 33 to 60

Age group	Twin pairs N	Both twins have OA N (%)	One twin has OA N (%)	Neither twin was OA N (%)
33–39All	1449	2 (0.1)	53 (3.7)	1394 (96.2)
MZ	514	0 (0.0)	21 (4.1)	493 (95.9)
DZ	935	2 (0.2)	32 (3.4	901 (96.4)
40–44 All	890	5 (0.6)	71 (8.0)	814 (91.5)
MZ	300	3 (1.0)	23 (7.7)	274 (91.3)
DZ	590	2 (0.3)	48 (8.1)	540 (91.5)
45–49 All	681	9 (1.3)	85 (12.5)	587 (86.2)
MZ	250	3 (1.2)	29 (11.6)	218 (87.2)
DZ	431	6 (1.4)	56 (13.0)	369 (85.6)
50–54 All	535	27 (5.0)	124 (23.2)	384 (71.8)
MZ	188	9 (4.8)	33 (17.6)	146 (77.7)
DZ	347	18 (5.2)	91 (26.2)	238 (68.6)
55–60 All	540	58 (10.7)	192 (35.6)	290 (53.7)
MZ	161	19 (11.8)	45 (28.0)	97 (60.2)
DZ	379	39 (10.3)	147 (38.8)	193 (50.9)
33–60 All	4095	101 (2.5)	525 (12.8)	3469 (84.7)
MZ	1413	34 (2.4)	151 (10.7)	1228 (86.9)
DZ	2682	67 (2.5)	374 (13.9)	2241 (83.6)
All men	1757	32 (1.8)	221 (12.6)	1504 (85.6)
All women	2338	69 (3.0)	304 (13.0)	1965 (84.0)

Twin pairs mailed detailed questionnaire in 1996 indicated by shading (see methods).

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reported whether they had ever been told by physician that they had OA.

In 1996 we mailed a questionnaire (available from authors upon request) to investigate OA in twins and their families; it was sent to those twin pairs of Finnish mother tongue of whom both were alive in 1996, and of whom both reported OA and aged 33 to 60 in 1990, and to those pairs of whom one twin reported OA and aged 33 to 54 in 1990. Of these 612 subjects, 560 (91.5%) responded to our questionnaire including 266 twin pairs (89 men pairs [43 MZ and 46 DZ] and 177 women pairs [80 MZ and 97 DZ]) in which both responded to the questionnaire. In addition there were 28 pairs of whom only one twin replied. This questionnaire included questions on physician diagnosed OA by joint, as well as occurrence of OA in the twins' parents and non-twin siblings. In the 1996 questionnaire we also asked for possible previous injuries (such as fracture, ligamentous or meniscal injury) that had preceded onset of the OA by joint, and current weight and height. Thus, BMI values and occupational loading data were available on most subjects from four occasions spanning 20 years, the last one being an OA-specific study.

Statistical analysis

When the number of unaffected twin pairs in the population is known as for the 1990 data, sophisticated models can be used to estimate the contribution of genetic factors to the susceptibility to OA. For complex disease, the multifactorial model is often used. It assumes that there is normally distributed liability to disease. When a certain level or threshold of liability is reached, the disease becomes manifest.[25] Both genes and environmental factors are assumed to contribute to the liability and they result from the joint effects of numerous genes with small effects and a spectrum of environmental effects. These assumptions were considered reasonable for this analysis based on prior knowledge of the genetics and environmental determinants of OA. Threshold models with additive genetic (A), dominance (non-additive) (D), shared environmental (C) or unique environmental (E) sources of variation in the underlying liability to disease can be fit. Shared effects are those environmental effects that are common to family members (twins), for example parental socio-economic status, whilst unique environmental factors are not shared (for example, adult occupational exposures). Various combinations of sources of variation can be fitted and the best fitting combination found, as described below. This permits assessment of the significance of additive genetic effects, effects due to dominance, and shared environmental effects to the variation in disease susceptibility in the population. The models are estimated based on zygosity-specific 2 by 2 contingency tables (disease present/absent in twin 1 vs disease present/absent in twin 2).[26]

Among the 1990 questionnaire responders, the correlation in liability to OA of any joint between the two members of MZ and DZ twin pairs was estimated by tetrachoric correlation, which is a correlation of a bivariate normal distribution that duplicates the cell probabilities from a 2 by 2 contingency table.[26] Structural equation modelling techniques with the Mx software package[27] were used to estimate variance components, their 95% confidence intervals, and compare different genetic models.

In the structural equation models, parameter estimates and goodness-of-fit statistics are computed as described in detail elsewhere.[26] The goodness-of-fit statistics assess to what degree the model specified by the investigators adequately corresponds to the data; a small goodness-to-fit χ^2 value and high P value indicates good correspondence between the model and data. Akaike's information criterion (AIC) is a statistic which combines information on the goodness-of-fit and the simplicity of the model.[26] The best model is thus generally the one with the lowest AIC value. Alternative models that specify different effects can be compared by assessing the change in χ^2 relative to changes in the degrees of freedom between models.[26] Heritability is a population-specific parameter, which gives the proportion of overall, phenotypic variance attributable to genetic factors.[28]

Among the 1996 questionnaire responders, we investigated joint-specific bilaterality of OA in the twins, and familial aggregation of OA in the parents and siblings of the twins. We further calculated joint-specific probandwise concordances[29] (affected individuals that belong to concordant pairs per all affected individuals that belong to either concordant or discordant pairs) of the reported OA by different joints.

Results

Occurrence of OA in 1990

In 1990, in 101 (2.5%) pairs both of the twins reported OA and one twin of 525 (12.8%) pairs reported OA, the prevalence of OA increasing expectedly by age (Table 1). A MZ male twin had an increased risk to have OA if his co-twin had OA (relative risk, RR 2.32; 95% CI: 1.10–4.88) compared with a twin whose co-twin did not report OA. Correspondingly, the risk was increased in DZ male twins (RR 1.51; 95% CI: 1.03–2.23), in MZ female twins (RR 3.12; 95% CI: 1.99–4.89) and DZ female twins (RR 1.53; 95% CI: 1.10–2.12).

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In male pairs the tetrachoric correlation coefficient for liability to osteoarthritis was 0.34 (SE 0.12) in monozygotic pairs and 0.38 (0.07) in dizygotic pairs. Model fitting indicated that the data were adequately accounted for (χ^2 = 2.09, P = 0.72) by a model with shared (non-genetic) familial effects accounting for 37% (95% CI: 24–49%) of the total variance in liability to the disease and unshared environmental effects accounting for 63% (95% CI: 51–76%). Models that included genetic effects fitted significantly worse (Table 2). In female pairs the tetrachoric correlation coefficient for liability to osteoarthritis was 0.62 (SE 0.07) in monozygotic pairs and 0.42 (0.06) in dizygotic pairs. Model fitting indicated that the data were best accounted for (χ^2 = 3.82, P = 0.28) by a model with additive gene effects explaining 44% (95% CI: 8–74%) of the variance in liability to the disease, and shared effects accounting for 20% (95% CI: 0–46%) and unshared environmental effects accounting for 36% (95% CI: 25–50%). Models that did not include genetic effects fitted significantly less well.

Joint-specific occurrence of OA in 1996

Joint-specific prevalences of reported physician-diagnosed OA in the 560 subjects responding to the 1996 questionnaire are shown in Table 3. The OA was reported to be bilateral most commonly in finger joints (Table 3). Of the 560 subjects, 422 were able to report whether their father, and 476 whether their mother, had OA which interfered with daily life. Except for twins with hip OA the prevalence of OA was usually higher in the parents, particularly in mothers, of those subjects who had OA (Table 4). This difference was most apparent with respect for OA of fingers. In the non-twin siblings of the twins, OA was more common in the siblings of those twins that had OA in their fingers than in the siblings of those twins that did not have OA in their finger joints (Table 4).

The pairwise occurrence of OA in the 266 pairs of twins, of whom both replied in 1996, is shown in Table 5. The probandwise concordances were highest for OA of the knees and fingers (Table 5). There were 16 pairs of whom both twins reported bilateral finger OA, the respective number of pairs being 1 for bilateral hip OA and 5 for bilateral knee OA. There were no twin pairs in which both reported bilateral ankle OA. If one of the twins had hip OA (unilateral or bilateral) 35.3% of the co-twins had OA in any joint, respective values being higher for other joints studied (knee 48.4%, ankle 64.7%, fingers 50.0%).

Factors predisposing to OA in discordant twin pairs

Based on the 1996 questionnaire there were 64 twin pairs discordant for hip OA and 70 twin pairs discordant for knee OA and 73 discordant for finger OA. Among the twin pairs discordant for OA of specific joints, previous injuries explained the occurrence of OA in two twin pairs discordant for hip OA, eight pairs discordant for knee OA and in five pairs discordant for finger OA.

Compared with the unaffected co-twin the body-mass index in 1975 tended to be higher in the twin with knee OA (mean difference 0.71, SEM 0.38, P = 0.068 by two-tailed paired t-test). This difference between the discordant twin pairs remained fairly similar from 1975 to 1996. There were no differences in body-mass index among twin pairs discordant for hip OA, and among twin pairs discordant for finger OA. Exclusion of twin pairs in which trauma explained the discordance changed these results only minimally.

Among the twin pairs discordant for hip and knee OA, the twin with OA reported in 1990 more

Table 2 Comparison of alternative genetic models fit to Finnish twin data on self-reports of physician-diagnosed osteoarthritis from the 1990 questionnaire. Univariate twin analysis for additive genetic (A) effects, common (C) shared environmental effects and environmental (E) effects unique to each subject

Model	Components of variance estimates			Goodness-of-fit tests		
	Additive genetic effects	Common (shared) environment	Unique environmental effects	χ^2	d.f.	AIC
Men						
1 ACE	0.00	0.37	0.63	2.09	3	–3.91
2 AE	0.49	–	0.51	6.49	4	–1.51
3 CE	–	0.37	0.63	2.09	4	–5.91
4 E	–	–	1.00	33.5	5	23.5
Women						
1 ACE	0.44	0.20	0.36	3.82	3	–2.18
2 AE	0.68	–	0.32	6.12	4	–1.88
3 CE	–	0.49	0.51	9.59	4	1.59
4E	–	–	1.00	104.7	5	94.7

AIC: Akaike's information criterion: a global measure of goodness-of-fit (see methods).

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commonly the occupational loading higher than that reported by the co-twin (Table 6), but the differences were less apparent in the reports in 1975. Among twin pairs discordant for finger OA there was no difference in the occupational loading between the co-twins.

Discussion

Based on our twin study, physician-diagnosed OA appears to be more often due to genetic effects in women than in men, and finger and knee OA show greater evidence of genetic contribution than does OA in the hip.

Our study was based on the subjects' reports on physician-diagnosed OA, which is usually based on clinical and radiographic examinations of symptomatic subjects, but standard radiographic grading is lacking. This limits the validity of our data even though there is no gold standard in the classification of OA.[30,31] This methodological compromise was accepted because we studied joint-specific familial aggregation of OA and it was not ethically acceptable to X-ray all the non-symptomatic joints of the subjects. Mild cases or misdiagnosed cases would tend to be missed leading to greater discordance in twin pairs. This should not affect analyses by zygosity. Also comparison of different joints within individuals is unlikely to be affected. In a study comparing self-report of common medical conditions including OA with medical records, Haapanen et al[32] found that self-report of hip or knee OA had a specifity of 88% and a sensitivity of 62%.

Among the whole study cohort, our data for women are consistent with those of Spector and colleagues,[13] who report that 41–46% of the variance in the narrowing trait score for all joints in their subjects was accounted for by additive genetic effects. In contrast, our results for men indicate that genetic effects may be modulated by sex or by environmental factors, such as occupational loading and injuries, distributed differently between men and women.

Among the responders to the 1996 questionnaire we found evidence for higher familial aggregation of OA of fingers and knees than of OA of hips. This is supported by high familial aggregation of OA, high bilaterality of OA and high concordance rate. A recall bias may exist in case of reporting co-occurrence of OA in family members. However, our finding agrees with early studies on the heredity of Heberden's nodes.[14,15] Based on earlier studies there is a higher prevalence of multiple joint OA in subjects with Heberden's nodes than in those without Heberden's nodes. Also, in the polyarticular

Table 3 Reported prevalence of physician-diagnosed osteoarthritis (OA) of specific joints among the 560 twin subjects responding to the questionnaire in 1996[a]

Joint	Bilateral (N, %)	Unilateral (N, %)	Total subjects with OA
Hip	36 (48.6)	38 (51.4)	74
Knee	57 (46.7)	65 (53.3)	122
Ankle	16 (42.1)	22 (57.9)	38
Fingers	90 (79.6)	23 (20.4)	113

[a]From 266 full twin pairs and 28 pairs with one responder.

Table 4 Occurrence of OA in the parents and non-twin siblings of the twin subjects according to the affected joint in the twin subjects

Affected joint in twin		Proportion of mothers with OA(%)[a]	P[b]	Proportion of fathers with OA (%)[a]	P[b]	Proportion of non-twin siblings with OA (%)[a]	P[b]
Hip	Yes	13.2	0.47	15.3	0.45	28.5	0.27
	No	10.6		11.9		23.2	
Knee	Yes	27.2	0.003	24.3	0.40	31.8	0.013
	No	15.5		20.0		21.8	
Ankle	Yes	8.8	0.030	6.3	0.96	41.4	0.040
	No	3.5		7.1		23.7	
Fingers	Yes	24.8	<0.001	26.1	0.053	41.2	0.0001
	No	12.4		17.0		19.6	

[a]% of the subjects able to respond to the specific question on the occurrence of OA in mother, father or non-twin sibling.
[b]P for difference in the occurrence of OA in the parents and in non-twin siblings by the occurrence of joint-specific OA in twin individuals (χ^2 test).

Table 5 Physician-diagnosed OA of specific joints and their probandwise concordances (Pw) among the 266 twin pairs in which both twins answered the questionnaire in 1996

Joint	MZ			DZ			All	
	One has OA	Both have OA	Pw	One has OA	Both have OA	Pw	One has OA	Both have OA
Hip	35	4	0.186	29	0	0.0	64	4
Knee	37	17	0.456	33	6	0.267	70	23
Ankle	20	2	0.167	11	1	0.154	31	3
Fingers	37	9	0.327	36	8	0.308	73	17

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Table 6 Occupational loading according to self-reports in 1975 and in 1990 (some pairs have missing data) among twin pairs discordant for OA of specific joints in 1996

	Occupational loading in twin with OA compared to the co-twin			P[a]
	Higher	Similar	Lower	
Hip OA				
1975	18	28	14	NS
1990	26	27	8	0.002
Knee OA				
1975	19	32	16	NS
1990	23	28	15	NS
Finger OA				
1975	16	33	21	NS
1990	19	35	15	NS

[a]By McNemar's test for discordant pairs.

disease, knees are often symptomatic but there is little evidence of an overabundance of hip OA in those with Heberden's nodes or generalised OA.[1,16,33,34] Our data are consistent with these studies and recent observations on a strong association between hand and knee OA.[35,36] Based on our data and earlier studies it seems evident that study series consisting of OA cases with primarily affected finger and knee joints would be most optimal targets to study genetic influence on the development of OA since they revealed the highest genetic component. Despite the relatively low clinical importance of interphalangeal OA, investigation of the associations between genetic variability and OA of the fingers offers a good model to investigate the genetic factors behind OA. Also, X-raying of finger joints does not expose individuals to high radiation doses. Previous occupational loading and injuries explained more of the discordance for knee OA than that of finger OA, which supports the idea that variation in the occurrence of knee OA, compared with finger OA, is explained more commonly by environmental factors. Though OA of the spine may also be a part of generalised OA, we considered that questionnaire-based study on spine OA is not valid due to the multifactorial etiology of back pain.

In conclusion, we investigated the twin and familial aggregation of OA overall and the differences in the aggregation by joint since exact knowledge of the joint-specific familial aggregation of osteoarthritis (OA) would be of benefit in determining the etiology of OA and in the planning of optimal study designs to define the genetic factors predisposing to the development of OA. Based on our data, genetic effects may be modulated by sex or by environmental factors distributed differently between men and women, because gene effects explained more of the variance in liability to OA in women than in men. Based on our joint-specific data it seems evident that OA specifically affecting finger and knee joints are most optimal targets to determine genetic influence on the development of OA.

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