Familial osteorarthritis : risk factors and determinants of outcome

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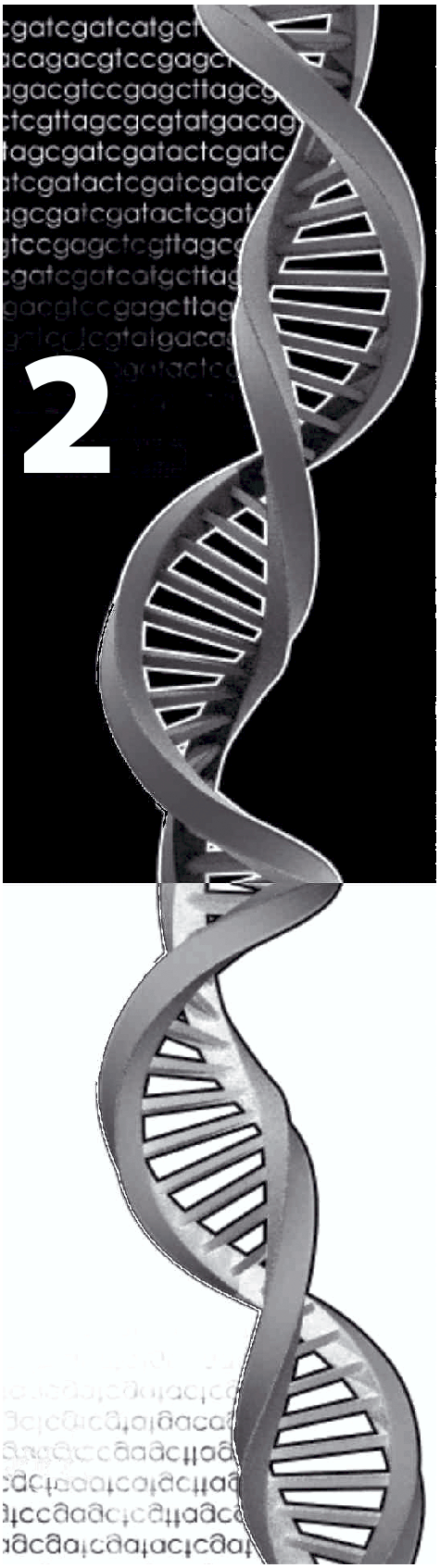

Evidence for familial aggregation of hand, hip and spine Osteoarthritis (OA), but not knee OA in siblings with OA at multiple sites. The GARP study

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Abstract

Objective

In a sib-pair study (Genetics, Arthrosis and Progression), consisting of patients with osteoarthritis (OA) at multiple sites we evaluated whether familial aggregation of OA differs by joint site.

Methods

The GARP study consists of Caucasian probands aged 40 to 70 and their siblings with primary OA at multiple sites. The diagnosis of knee, hip and spine OA was based on a combination of pain or stiffness on most days of the last month and the presence of osteophytes or joint space narrowing on X-ray. Hand OA was defined by the American College of Rheumatology criteria. We calculated odds ratios (OR) for sib and proband sharing disease in the same joints.

Results

We included 191 sib-pairs (85% women, mean age 60 years). In the probands OA was present in: spine (76%), hands (77%), knees (37%) and hips (26%). The most common OA combinations in probands were: spine-hand (59%), spine-knee (27%) and hand-knee (25%). The OR adjusted for age, sex and body mass index (BMI) with 95% confidence intervals (CI95) for siblings to be affected in the same joint site(s) as the proband were increased in OA of the: hand 4.4 (CI95 2.0-9.5), hip 3.9 (CI95 1.8-8.4), spine 2.2 (CI95 1.0-5.1), hip-spine 4.7 (CI95 2.1-10.4) and hand-hip 3.4 (CI95 1.1-10.4). Siblings of probands with OA in the knee did not have an increased likelihood of knee OA.

Discussion

In middle-aged patients with familial OA at multiple sites, familial aggregation of OA was most striking for hand and hip OA but remarkably absent for knee OA.

Key words

Osteoarthritis, GARP, sibpair and genetics

Osteoarthritis (OA) is a debilitating disease of joint cartilage destruction and changes in the adjoining bone margins. The exact pathogenesis of OA is still unknown. Age and sex are strong determinants of OA occurrence in all joint groups. For other determinants, such as body mass index (BMI) and occupation, the impact differs by joint site (1). This suggests the presence of subtypes of OA with different mechanisms for different sites. Apart from the role of environmental determinants in OA, a hereditary basis has been documented already in the 1940s by Stecher and was later confirmed and extended by Kellgren et al (2,3). Stecher found a two to three fold risk of the presence Heberdens nodes in mothers and sisters of probands with Heberdens nodes (2). Kellgren et al. found that first-degree relatives of probands with generalized OA had a two-fold increase of OA compared with population controls (3).

In several subsequent studies familial aggregation has been reported for hand (2, 4), knee (5), hip OA (6, 7) and disc degeneration (8, 9). The majority of studies on hand and knee OA concerned subjects with radiographic OA rather than symptomatic OA and focused on the familial clustering of one joint site while no information was collected on OA characteristics of the other joint sites in the same subjects. Studies that investigated the familial aggregation of polyarticular OA based on the combination of affected joint sites yielded inconsistent results. Familial aggregation has been reported of radiographic hand OA in combination with knee OA (10, 11), of hand OA in combination with hip OA (12, 13) and of hand OA in combination with disc degeneration (8). The study of Bijkerk et al (8) was the only study that included radiographic information of all four sites (hands, knees, hips and spine) and familial aggregation of hand with knee or of hip OA could not be confirmed. Heritabilities ranging from 10 to 70% were reported for disease at the various joint site(s) (5, 9, 10). It is unclear whether the varying heritabilities imply that the genetic contribution to OA is joint-related or whether it is the result of heterogeneous phenotype definitions and study designs, or different prevalences of acquired risk factors.

In the present study we investigated in a well-documented sib-pair study with middle-aged patients with symptomatic OA, radiographically confirmed, at multiple sites, the familial aggregation of OA at specific joint sites (hands, knees, hips and spine) and combination of joint sites.

Patients and Methods

The present study is part of the ongoing GARP study (Genetics, Arthrosis and Progression). The GARP study is aimed at the identification of determinants of OA susceptibility and progression. The study is based on Caucasian sib-ships of Dutch ancestry with predominantly symptomatic OA at multiple sites.

Recruitment and clinical evaluation

Patients (probands) aged between 40 to 70 with symptomatic OA in the hands, knees or hips, diagnosed by rheumatologists, orthopaedic surgeons and general practitioners in Leiden, The Hague, Delft, Haarlem and Amsterdam were informed of the ongoing study by mail. Interested probands

were subsequently sent a mailed questionnaire about demographic data, medical history, symptoms and signs of OA and family history of OA. Subsequently probands with OA at multiple sites with a positive family history were requested to introduce a sibling "with joint complaints", who was also addressed by a mailed questionnaire. After obtaining informed consent, all sib-ships underwent a physical examination and were assessed by a single medical doctor (NR) at the outpatient clinic. Questionnaires were verified and data were collected on physical functioning and quality of life. The two questionnaires used to assess physical functioning, were the Western Ontario and Mac Master Universities OA Index (WOMAC) and the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index. These questionnaires contain questions on pain, stiffness and disability as a result of day-to-day activities in respectively the lower extremities and the hands.

Patients with secondary OA and familial syndromes with a Mendelian inheritance pattern were excluded. Considered as secondary OA were: 1) major congenital or developmental diseases and bone dysplasias, 2) major local factors such as severe scoliosis and hypermobility, 3) certain metabolic diseases associated with joint disease such as hemochromatosis and Wilson's disease, 4) inflammatory joint diseases such as rheumatoid arthritis, 5) other bone diseases such as morbus Paget and osteochondritis, 6) intra-articular fracture. Patients with a shortened life expectancy were also excluded. Ccrystal deposition arthropathies (unless in the case of severe polyarticular gout), and diabetes mellitus or thyroid conditions were not considered as exclusion criteria.

OA diagnosis

Probands and siblings were included in the GARP study with OA at multiple joint sites in the hands or with OA in two or more of the following joint sites: hand, spine (cervical or lumbar), knee or hip. Both subjects were required to have symptomatic OA (as defined below) in at least one joint site. Subjects with symptomatic OA in just one joint site were required to have structural abnormalities in at least one other joint site defined by the presence of radiographic OA in either of the four joints or the presence of two or more Heberden nodes, Bouchard nodes or squaring of at least one CMC1 joint on physical examination.

Symptomatic OA in the knee and hip was defined following the American College of Rheumatology (ACR) recommendations for knee and hip OA (14, 15). Knee OA was defined as pain or stiffness for most days of the prior month and osteophytes at joint margins of the tibiofemoral joint (x-ray spurs). Hip OA was defined as pain or stiffness in the groin and hip region on most days of the prior month in addition to femoral or acetabular osteophytes or axial joint space narrowing on radiograph. Joint prosthesis in the hips or the knees as a result of end stage OA was included as OA in that particular joint. Spine OA (cervical and lumbar) was defined as pain or stiffness on most days of the prior month in the spine in addition to a Kellgren-Lawrence score of two in at least one disc or one apophyseal joint. OA in hand joints was defined according to the ACR criteria (16) as pain or stiffness on most days of the prior month in addition to 3 of the following 4 criteria: bony swelling of 2 or more of the 10 selected joints [bilateral DIP joints 2 + 3, bilateral PIP joints 2 + 3 and CMC 1 joints], bony swelling of 2 or more DIP joints, less than 3 swollen MCP joints and deformity of at least 1 of the 10 selected joints. A sub-analysis was performed for OA in

the different hand joints. DIP, PIP (which included the IP joint) and CMC1 OA were defined by pain or stiffness on most days of the prior month in each joint site in addition to a Kellgren-Lawrence score of at least 2 in the corresponding joint site.

Radiographs

Conventional radiographs of the hands (dorso-volair), knees (Posterior-Anterior in weight bearing (PA) / semi flexed and lateral), hips (PA), lumbar (PA and lateral) and cervical spine (Anterior-Posterior, lateral and transbuccal) were obtained from all participants. This was performed in a standard manner with a fixed film-focus distance and a fixed joint position. Conventional radiographs of the knees were made by using the fixed-flexion radiography as recommended by Peterfy et al (17). All radiographs were performed by a single experienced radiology technician. Conventional radiographs were scored by a single experienced musculoskeletal radiologist (HK) for osteophytes in the knees and hips and joint space narrowing in the hips. In addition to the hands (DIPs, PIPs and CMC1), the discs and apophyseal joints of the cervical and lumbar spine, the hips and tibiofemoral joints of the knees were also scored according to the Kellgren-Lawrence scale with the help of the original atlas (18). This is a five scale scoring system with ascending severity based on the presence of osteophytes, joint space narrowing, sclerosis and degenerative cysts. A Kellgren-Lawrence score of ≥ 2 depicts OA in a particular joint.

The intra-reader variability for the different joint sites, scored by the Kellgren-Lawrence method, depicted by the intra-class correlation-coefficient (ICC) (95% confidence interval) was for the hands 0.95 (0.92-0.96), for the knees (tibio-femoral) 0.92 (0.86-0.96), for the hips 0.95 (0.92-0.98), for the cervical spine (apophyseal and disc) 0.71 (0.52-0.84) and for the lumbar spine (apophyseal and disc) 0.67 (0.46-0.81). The intra-reader variability was based on the examination of 40 radiographs, which were selected randomly throughout the duration of the study period and were blinded for any patient characteristics.

Statistical analysis

OA at each site was dichotomised according to the presence or absence of OA. We calculated odds ratios (OR) for joint disease involving a particular site in the siblings, given the same joint site in the proband. An OR > 1, in our study, indicates that probands and siblings share disease at the same sites more often than expected form the overall distribution of joint sites with disease. ORs are presented with a 95% confidence interval (CI95) according to the method of Woolf. Unconditional logistic regression analysis was used to adjust for the most important risk factors of OA: age, sex and BMI. The Mann-Whitney U test was used for the comparison of the different types of OA in probands and siblings.

Table 1. Characteristics of probands and siblings with familial OA at multiple sites of the 191 sib-pairs included in the GARP study.

	probands	siblings
Women n (%)	162 (85)	150 (79)
Age mean (range)	59.9 (46-76)	60.6 (43-79)
BMI median (range)	26.9 (20-46)	26.2 (19-46)
Structural abnormalities at multiple sites	191 (100)	191 (100)
Symptomatic OA at multiple sites	178(93)	166 (87)
Pain or stiffness at multiple sites	185 (97)	187 (98)
WOMAC[1] 0-100 median (range)	27.3 (0-95)	18.7 (0-88)*
AUSCAN[2] 0-60 median (range)	19.0 (0-59)	15.0 (0-54)*

*significant difference between probands and siblings at $p<0.05$

[1]Western Ontario and Mac Master Universities OA Index

[2]Australian/Canadian Osteoarthritis Hand Index

Table 2. Frequency of symptomatic osteoarthritis (OA) at the various joint sites in the probands and siblings with familial OA at multiple sites of the 191 sib-pairs included in the GARP study.

	probands (%)	siblings (%)
Affected sites with symptomatic OA		
hand	148 (77)	128 (67)*
DIP[1] or PIP[2] or CMC1[3]	127 (66)	113 (59)
DIP	93 (49)	74 (39)*
PIP	81 (42)	66 (35)
CMC1	57 (30)	47 (25)
spine	145 (76)	159 (83)
hip	49 (26)	44 (23)
knee	70 (37)	60 (31)
Combination of sites with symptomatic OA (%)		
hand-spine	112 (59)	105 (55)
hand-knee	48 (25)	34 (18)
hand-hip	28 (15)	23 (12)
knee-spine	51 (27)	53 (28)
hip-spine	39 (20)	39 (20)
hip-knee	16 (8)	13 (7)

*significant difference between probands and siblings at $p<0.05$

[1] Distal interphalangeal joint

[2] Proximal interphalangeal joint

[3] first carpometacarpal joint

Results

Recruitment

Of the 1874 probands identified from the various practices, 833 responded (44%). Of the 833, 521 probands reported a positive family history for OA in first-degree relatives. Of these probands, 353 had at least one sibling with joint complaints. One hundred and thirty nine of these siblings were either unwilling (n=92) to participate or they did not meet the GARP criteria (n=47). This resulted in the recruitment of 214 eligible sib-ships.

Between August 2000 to March 2003, 212 probands and 224 siblings were screened at the outpatient clinic. After a clinical and radiographic evaluation, 191 probands and 202 siblings met the GARP criteria. For the present study, in sib-pairs with additional siblings, the youngest sibling with OA at multiple joint sites was included.

The characteristics of the 191 sib-pairs are shown in table 1. The majority of the probands and their siblings were female. Age and BMI were similar in probands and siblings. All probands and siblings had structural abnormalities in at least two joint sites. One hundred and seventy eight (93%) probands and 166 (87%) siblings had symptomatic OA at multiple sites. Ninety seven percent of the probands and 98% of the siblings had pain or stiffness at multiple sites. The median WOMAC score and the median AUSCAN score in probands representing a sum score of pain, stiffness and disability in respectively the hands and lower extremities were higher in the probands than in the siblings

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Familial aggregation

Table 2 shows the frequency of symptomatic OA at the various joint sites. These were generally equally distributed between probands and siblings, except for OA in the hand joints, which was less frequent in siblings than in probands: OR = (0.59, CI95 0.4-0.9). Of the 93 probands and siblings with hip OA, 38 had a hip prosthesis, 45 had joint space narrowing as well as osteophytes, 8 had osteophytes with no joint space narrowing and only 2 had joint space narrowing without osteophytes. Eight probands and 3 siblings had knee prostheses. The three most common combination of symptomatic OA in the probands was that of OA in the hand joints in combination with OA in the spine (59%), knee with spine OA (27%) and hip with spine (20%). In siblings we found similar results.

In table 3 the odds ratios are given for site sharing. When probands had hand OA, siblings had an increased risk to have symptomatic OA in the hands (crude OR =3.5 CI95 1.7-7.1) (adjusted OR=4.4 CI95 2.0-9.5). This was also found for the hips (crude OR =5.1 CI95 2.5-10.6) (adjusted OR=3.9 CI95 1.8-8.4) and spine (OR=2.2, CI95 1.0-5.0). Adjustment for age, sex and BMI did not change the estimate for spine OA. When the familial aggregation of OA in the apophyseal joints was regarded separate from disc degeneration, this estimate was not affected. However, when the proband had involvement of the knee, the sibs did not have an increased likelihood of knee disease. Concordance was most striking for bilateral hip OA: siblings of probands with bilateral hip OA had a

Table 3. The odds ratio's (OR) of site sharing (symptomatic OA) in patients with familial OA at multiple sites, expressed as crude and adjusted odds ratio's (95% confidence interval) for age, sex and body mass index in the 191 sib-pairs included in the GARP study

OA sites		sib OA +	sib OA-	crude OR (95%CI)	adjusted OR (95%CI)
Hand	proband OA +	109	39	3.5 (1.7-7.1)	4.4 (2.0-9.5)
	proband OA -	19	24		
DIP[1] OA		45	48	2.2 (1.2-4.0)	2.3 (1.2-4.4)
		29	69		
PIP[2] OA		35	46	1.9 (1.1-3.6)	1.8 (1.0-3.4)
		31	79		
CMC[3] OA		21	36	2.4 (1.2-4.8)	2.6 (1.2-5.4)
		26	108		
Spine		125	20	2.2 (1.0-5.0)	2.2 (1.0-5.1)
		34	12		
Hip		23	26	5.1 (2.5-10.6)	3.9 (1.8-8.4)
		21	121		
Knee		23	47	1.1 (0.6-2.1)	1.0 (0.5-2.0)
		37	84		

[1] Distal interphalangeal joint

[2] Proximal interphalangeal joint

[3] first carpometacarpal joint

Table 4. Concordance between probands and siblings for the combination of two affected joint sites with symptomatic OA in patients with familial OA at multiple sites, expressed as crude and adjusted odds ratio's (95% confidence interval) for age, sex and body mass index in the191 sib-pairs included in the GARP study

OA sites		sib OA +	sib OA-	crude OR (95%CI)	adjusted OR (95%CI)
Hand-spine	proband OA +	65	47	1.3 (0.8-2.4)	1.5 (0.8-2.7)
	proband OA -	40	39		
Hand-hip		7	21	3.1 (1.1-8.3)	3.4 (1.1-10.4)
		16	147		
Hand-knee		6	42	0.6 (0.2-1.5)	0.6 (0.2-1.7)
		28	115		
Knee-hip		2	14	2.1 (0.4-10.6)	1.7 (0.3-9.2)
		11	164		
Knee-spine		12	39	0.7 (0.4-1.6)	0.7 (0.3-1.6)
		41	99		
Hip-spine		18	21	5.3 (2.5-11.7)	4.7 (2.1-10.4)
		21	131		

8.1-fold increased risk of also having hip OA (crude OR= 8.1, CI953.1-21.0), (adjusted OR=6.9 CI95 2.6-18.7). Restriction to female sib-pairs (n=254), led to similar results. Further, when analysis was restricted to the 156 probands and siblings with symptomatic OA at multiple sites, these estimates were not materially affected. Additional adjustment in site sharing for exposure to jobs entailing strenuous physical labor did not affect these results.

Table 4, shows the concordance between probands and siblings for the combination of two affected joint sites with symptomatic OA. Concordance was highest for the combination of hip-spine followed by hand-hip. Siblings of probands with OA in the hips in combination with the spine had a 5-fold increase of having OA at the same joint sites: (crude OR =5.3 CI95 2.5-11.7) (adjusted OR=4.7 CI95 2.1-10.4). Siblings of probands with OA in the hips in combination with the hands had a 3-fold increase of also having OA at the same sites: (crude OR= 3.1 CI951.1-8.3) (adjusted OR=3.4 CI95 1.1-10.4).

Discussion

Among middle-aged patients with familial OA at multiple sites, siblings tend to be affected in the same joint sites, particularly for OA in the hips, hands and spine but not for knee OA.
In the present study, in a patient population with predominantly symptomatic OA at multiple sites, the familial aggregation was most prominent for hip OA and hand OA. Familial aggregation of hip OA has been suggested in other studies, however, not in the context of OA at multiple sites. In most of these studies, the hip was the only joint site under investigation. Four studies have examined the prevalence of OA among relatives of cases who had undergone total hip replacement surgery, a surrogate for severe disease. Lindberg (19) showed that the frequency of radiological OA among siblings of 184 probands was twice as high as in the general population. Chitnavis (20) et al found a slight increase of a recalled diagnosis of hip OA among relatives of 402 probands undergoing total hip replacement surgery compared to controls. Lanyon et al (6) found a four-fold risk for hip OA among siblings of 398 probands with total hip replacement surgery compared with population-based controls. Ingvarsson et al (21), found that siblings of 2713 probands who had undergone total hip replacement surgery for hip OA, were three times more likely to require total hip replacement surgery than matched population controls. Data on the familial aggregation for radiographic OA is less consistent. MacGregor et al (7), found in a twin study, that genetic factors have a substantial contribution (up to 60% of the total variance) in radiographic hip OA. The other study investigating radiological OA at multiple sites by Bijkerk et al (8), no statistically significant genetic effect was found for radiological hip OA in siblings of 118 probands with OA at multiple sites drawn from a random population of 1583 individuals. It should, however, be noted that in the study of Bijkerk et al, the number of subjects with hip OA was too small to accurately measure heritability.
It is unlikely that the familial aggregation of hip OA in the present study can be attributed to developmental abnormalities such as dysplasia since the majority of patients had complaints of OA at

multiple sites and great care was taken to exclude patients with possible secondary OA by excluding all patients with intra-articular fractures and patients with dysplasia of the hips.

The influence of hereditary factors in hand has been consistently reported in various studies (2, 3, 4, 10, 11). Our results confirm these findings. When the separate hand joints are examined, our data are conform to the study of Jonsson et al. (4) in 2,919 patients with hand OA, who found that the genetic influence to be present in the IP joints as well as the first CMC joint.

The familial aggregation of OA in the apophyseal joints of the spine has not been previously studied. In GARP, diagnosis of spine OA was based on the presence of OA in the apophyseal joints or the presence of disc degeneration in combination with symptoms. The inclusion of disc degeneration in the OA definition used in GARP was prompted by the finding by Bijkerk et al (8), who found disc degeneration to have a strong familial component. An important genetic influence on variation in disc degeneration was also found by Sambrook et al (9) in a Magnetic Resonance Imaging (MRI) study with 154 dizygotic twins.

In contrast to the majority of studies showing significant heritability of radiological characteristics of knee OA either isolated or in combination with hand OA no aggregation of knee OA was found in the GARP sib-pairs (5, 10, 11). Familial aggregation for knee OA was first found by Spector (5) in a cohort of female twins, with a heratiblity of 39%. Two segregation studies by Hirsch et al (10) and Felson et al (11), found familial clustering of poly-articular OA consisting of hand and knee OA. There are several possible explanations for the discrepancy between our findings and the findings in these studies. The crucial difference between ours and previous studies is that we focused on symptomatic disease in combination with radiology, rather than radiological findings alone. In GARP, only those patients were included with OA symptoms at multiple sites, therefore, familial aspects of isolated knee OA would go undetected in our study. The familial aggregation reported by Hirsch (10) and Felson et al (11) may be dominated by the effects in the hands since the analysis was based on the sum score of the affected joints in the hands and knees. The reported heritability values are influenced by the greater number of joints that can be affected in the hands, than in the knees. Further, the patellofemoral joints were not included in our study in contrast to the study by Spector et al (5), possibly leading to the underestimation of symptomatic knee OA in GARP. The absence of familial influences on knee OA in GARP as compared to other joint sites may be due to environmental factors that have been suggested to play a more important role in the development of knee OA than that of hip and hand OA. This is supported by the various studies that report the strongest association of factors such as BMI and mechanical stress with knee OA (22-26).

In the present study, we found that siblings of probands with OA in the combination of spine and hip and hand and hip to be at an increased risk of developing OA in similar joint sites. The familial clustering of hand-hip was found earlier by other investigators (12, 13). No familial clustering was found for hand and knee OA in contrast to the study by Felson (11) and Hirsch et al (10). In the population-based study by Bijkerk et al (8), a significant familial clustering was found of hand and disc degeneration in the spine (thoracic and lumbar). We could not confirm these findings. Different case definition and different joint sites in the spine may have contributed to this discrepancy.

The patient population included in the GARP study represents a population with symptomatic

familial OA at multiple sites with a relatively early onset between the ages 40 to 70 years. To our knowledge the prevalence of this OA phenotype in the population, has not been established. In the Rotterdam population-based study, generalized radiological OA has been reported to occur in 14% of the population aged 55-65 (personal communication). Symptomatic OA is in general less frequent than radiological OA, so a prevalence of less than 14% seems realistic. Moreover inclusion criteria in the GARP study also requires a familial aspect of OA. Familial OA at multiple sites is not representative of general OA and the results from the GARP study may not be generalized to all OA phenotypes, although this phenotype is important as it can provide us with insight in the etiological determinants of OA in general.

The response rate in the present study was 44%. This may be partly attributed to the recruitment procedure in the present study. In order to get in touch with the subjects that met the study criteria, several steps had to be undertaken. All OA patients with hand, knee or hip involvement were contacted by mail stating the familial aspect of this study. It is conceivable that patients, who did not meet the criteria, did not respond. Furthermore the low response rate may also be partly due to the low prevalence of this OA phenotype in the population. That the response rate is not a reflection of the response rate among subjects that met our criteria is further supported by a higher response rate of 70% of the siblings.

The question that now arises is whether the selection procedure in GARP might somehow have influenced the familial aggregations found in the present study. We do not believe that this is the case, since the results in the present study would have been biased only when siblings were recruited when they had OA at the same site as their probands, which was not the case.

Our results show joint specificity in the familial aggregation of OA in sib-pairs with symptomatic OA at multiple joint sites. Within this study population the familial influences are most remarkable for OA in the hip and the combination of hip and hand OA and lowest for OA in the knee. Our results in the context of existing knowledge indicate that genetic mechanisms may be revealed contributing to the development of OA phenotypes based on isolated hip OA or hip OA in the presence of a much more generalized phenotype. It is possible that genetic heterogeneity may underlie these different clinical endpoints.

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