How Important Are Genetic Factors in Osteoarthritis?

MICHAEL DOHERTY

The recognition of an hereditary component to osteoarthritis (OA) is not new. In 1881, Charcot[1] commented that Heberden's nodes were "...a hereditary disease [that] may appear in several members of the same family." In 1889, Duckworth[2] observed a strong female predominance in 4 generations within a family. A number of reports[3-5] subsequently confirmed the familial occurrence of Heberden's nodes, and especially of a phenotype that was symptomatic in relatively young individuals. The first formal study of Heberden's nodes was undertaken by Stecher, *et al*[6,7], who described 74 people who had multiple Heberden's nodes bilaterally and, examining the families of these individuals, found an incidence twice as high as expected in the mothers and 3 times as high in the siblings. He concluded that Heberden's nodes were probably the result of a single autosomal gene that was dominant in women and recessive in men.

Some time after those initial observations, a case study in Manchester, England, examined the familial association of nodes and the relationship of nodes to OA at other sites. Kellgren, *et al*[8] conducted a marvelous epidemiologic study, taking mobile radiographic equipment into the community in the middle of England, to examine the prevalence of radiographic OA at a variety of joint sites. After having established the background prevalence of radiographic OA, he and his colleagues examined 52 index cases (defined as people who had OA at multiple joint sites) and their first-degree relatives who were over the age of 45 years, and compared the prevalence of OA in them to the prevalence of OA in the general population. Multiple joint OA was found to be more than twice as common in the relatives — mainly in females and older relatives — as in the general population, although its prevalence was significantly increased also in male relatives. Further, nodes were found to be co-associated with multiple joint OA, leading the investigators to call this condition "nodal generalized OA." However, in people who had multiple-site OA with Heberden's nodes, the distribution of OA was slightly different from that in people who had multiple joint OA without nodes. The nodal group presented a classic phenotype that is recognized widely, mainly targeting distal and proximal interphalangeal joints and the thumb base. Those who did not have nodes often exhibited a slightly different distribution, with involvement of the metacarpophalangeal joints and wrists and more inflammatory disease. Notably, hip joint OA was not a prominent feature of this multiple joint OA with familial predisposition.

A number of problems confront those trying to conduct genetic family studies in OA, especially the late age of expression of the phenotype, which makes vertical family studies extremely difficult. Radiographs are the main tool available for the assessment of structural change in OA, but unfortunately radiographic assessment is very insensitive for detection of early changes in cartilage and bone. Further, Heberden's nodes may not be strongly linked to single-joint OA at other sites. The quantification of structural changes is fraught with problems, with respect to assessment of joint space narrowing and osteophytosis. Should a case definition of OA require a combination of these? Should we look more broadly at other features that can be recognized on the radiograph, such as whether the bone response is atrophic or hypertrophic? We recognize that the clinical phenotype of OA is very heterogeneous. Should we lump hand disease together with knee disease and hip disease? Should we study them separately or examine combinations? Even within the same joint, for example the knee, OA of the patellofemoral and medial tibiofemoral compartments may have different associations. Should we call them all "knee OA." regardless of the compartment involved, or study them as discrete entities? Severity is a difficult issue that also poses problems. For example, is OA that begins early in life a more severe form than that which begins in older individuals? Is it the rate at which OA progresses that defines its severity? If one knee is affected, is this really more severe than if 5 finger joints are affected?

As indicated above, the study of such a heterogeneous disorder carries numerous problems. Of course, this has not stopped people from attempting to work through the question of how important genetics are to OA. However, whenever we hear data on this topic, the above caveats should be borne in mind.

Three main strategies have been used to examine the role of genetics in OA:

1. Classic twin studies, in which we identify as many monozygotic and dizygotic twins as possible and look at concordance within the 2 groups with respect to OA. Obviously, the higher the concordance between monozygotic compared to dizygotic twins, the greater the likelihood of a genetic contribution to OA.
2. Another approach is to identify subjects with clinically severe disease, for example, severe enough symptoms to lead to total joint arthroplasty (TJA), and to compare the

From the University of Nottingham Medical School, Nottingham, United Kingdom.

M. Doherty, MD, FRCP, Professor of Rheumatology.

Address reprint requests to Prof. M. Doherty, Academic Rheumatology, Clinical Sciences Building, City Hospital, Hucknall Road, Nottingham NG5 1PB, England.

prevalence of OA in their siblings (who have a genetic exposure) with that in controls who are matched as closely as possible to the siblings with respect to other epidemiologic, constitutional, and environmental risk factors.

3. A third approach is to examine within families the vertical segregation of OA into the next generation or the horizontal aggregation of the disease, as reflected by the concordance between siblings. A variant of this is to study inheritance of OA within a community in which the lineage of all families is known. This opportunity rarely presents itself but has been undertaken in places like Iceland and Newfoundland. Iceland provides an excellent model for this because the genealogy of the entire community has been carefully recorded since Iceland was first populated, and the mispaternity rate evident from DNA "fingerprinting" is extremely uncommon, making it possible to look backward and sideways through many generations. It is thus possible to see the relatedness of each individual to the others and to identify those families with the highest prevalence of OA.

What have we gleaned from the application of these main strategies?

Twin studies. Several classic twin studies have been performed, but the best known and one of the largest is the study by Tim Spector's group at St. Thomas Hospital, London, UK[9]. These investigators have assembled a large number of monozygotic and dizygotic twin sets and have reported much higher interclass correlations in monozygotic compared to dizygotic twins for a large variety of features that we would recognize as being relevant to OA (e.g., Heberden's nodes, knee pain, joint space narrowing, osteophytes). The heritability of OA, i.e., how much of the variance in the distribution of OA might be attributable to genetic, rather than constitutional or environmental factors, can be calculated in these twin sets after adjustment of the data for other known risk factors such as age, sex, and body mass index (BMI). Heritability for OA has been found to be high at all sites examined, the estimate ranging approximately from 40% to 60%[10,11].

A few concerns exist, however, about twin studies. Monozygotic twins may share their environment to a much greater extent than dizygotic twins. That is certainly true *in utero*. We are becoming increasingly aware that intrauterine growth may relate to subsequent chronic disease whose onset is in adulthood. Also there is a concern that monozygotic twins, to a greater extent than dizygotic twins, may share environmental factors in lifestyle even when they reach adulthood. Such caveats, however, are mainly theoretical, and it is highly unlikely that bias of this type explains the very large genetic influences being observed.

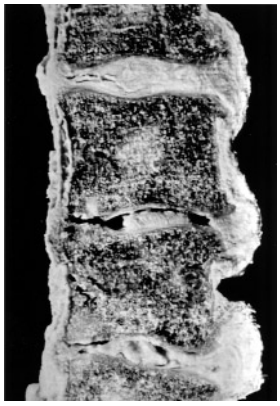
Sambrook, *et al*[12] (Figure 1) examined the cervical and lumbar spine in their twins by magnetic resonance imaging (MRI), and have combined their twin data set from St. Thomas Hospital with that from a large twin registry in Australia. Their analyses indicated that the heritability of MRI changes in the intervertebral discs (e.g., disc height, disc bulge, anterior osteophytes) was extremely high (approximately 60–80%) in both the cervical and lumbar regions. Interestingly, heritability was readily apparent for disc height and disc bulge, but not for an abnormal MRI signal, which relates to the water content in the disc. Thus, some aspects of disc disease may be influenced more by environment than by heredity.

Probands undergoing hip or knee arthoplasty for OA. What information can we derive from studies of large joint OA in patients presenting for TJA? In some of these studies, the phenotype used has been TJA, irrespective of the radiographic appearance of the joint. Lindberg[13] was the first to report an increased prevalence of hip OA of 8% in 289 siblings of patients who had undergone TJA for hip OA, compared to the 3.8% prevalence in matched control subjects. However, there were many caveats to this study, especially that only pre-existing radiographs of siblings were used and these had been undertaken largely to investigate hip pain.

In a more recent study in Oxford, in which patients who had had total hip arthroplasty (THA) or total knee arthroplasty (TKA) were identified, the frequency of self-reported joint replacement in the siblings was ascertained by postal questionnaire and was compared with that in the spouses of the index cases. The relative risk for a joint replacement in the sibling was very high — 2.32, 95% confidence interval (CI) 1.22–4.43. The risk for TKA was as high as 4.80 (0.64–36.4), while that for TKA was 1.86 (0.93–3.69)[14]. Important caveats to this study include absence of data on preoperative hip radiographs and the use of spouses as controls with potential bias relating to non-assortative mating.

Figure 2 provides data from a similar study undertaken by our group, in which we identified index cases of hip OA who had undergone THA in Nottingham, UK. We contacted all adult siblings who were available in Nottinghamshire and asked them to come in for a radiograph, regardless of whether they had symptoms[15]. We compared the prevalence of radiographic hip OA in these siblings to the prevalence of radiographic hip OA in subjects undergoing intravenous urograms for investigation of a renal problem which, theoretically, would have neither a positive or negative effect on the risk of hip OA.

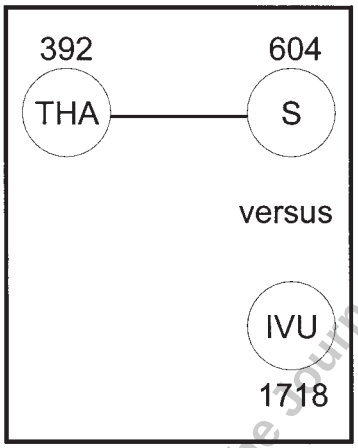
Regardless of the definition of radiographic OA we employed, after adjustment for other risk factors known to be important for hip OA we found the relative risk of radiographic hip OA in siblings higher than in the general population. The relative risks were higher in men than in women. The risks of having bilateral, rather than unilateral hip OA, and THA, were also higher in the siblings. Interestingly, the presence of Heberden's nodes or obesity did not influence the risk for radiographic hip OA. Thus, as in the previous



- MRI of cervical and lumbar spine
  172 MZ, 154 DZ (male + female)
- aH^2 (age, weight, height, smoking, physical activity)

	cervical spine	lumbar spine
disc height	0.65 (0.53-0.73)	0.79 (0.71-0.84)
disc bulge	0.59 (0.44-0.70)	0.65 (0.51-0.74)
osteophyte	-	0.54 (0.38-0.66)

Figure 1. Results of MRI studies of the cervical and lumbar spine in 172 monozygotic (MZ) and 154 dizygotic (DZ) twins. aH^2: heritability. After adjustment for age, weight, height, smoking and physical activity, heritability (aH^2) of disc height and disc bulge and contra was extremely high in both the cervical and lumbar spine, and heritability of osteophyte was high in the lumbar spine. However, heritability was not apparent for an abnormal MRI signal related to the water content of the disc. Adapted from Sambrook, *et al*. Arthritis Rheum 1999;42:366-72.



- increased aOR in siblings

≤ 2.5 mm	5.03 (3.93-6.46)
≤ 1.5 mm	6.21 (4.36-8.84)
bil. ≤ 2.5 mm	5.86 (3.95-8.68)
grade 3-5	7.12 (6.45-9.31)
THA	9.76 (5.74-16.6)

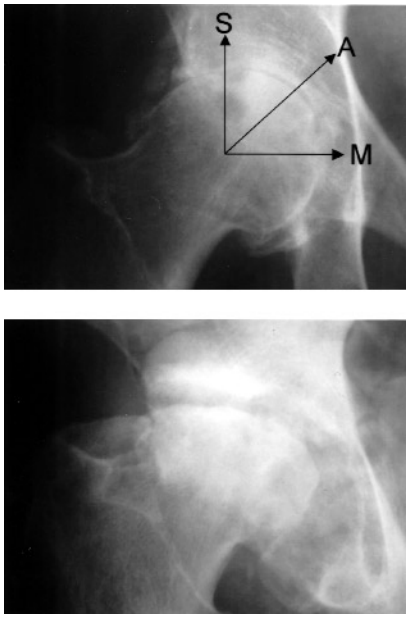
- higher in men
- Heberden's nodes, BMI – no influence

Figure 2. Hip OA sibling study. aOR: adjusted odds ratio, S: siblings of patients who had undergone total hip arthroplasty (THA); IVU: subjects undergoing intravenous urograms, whose radiographs were examined for the prevalence of hip OA (see text). BMI: body mass index. aOR is shown for various degrees of joint space width, in mm; for bilateral definite hip OA; for Croft grade of severity of hip OA; and for THA (see text). Adapted from Lanyon, *et al*. BMJ 2000;321:1179-83.

studies, we identified a very strong familial risk of radiographic hip OA, particularly bilateral OA, in siblings of subjects who had undergone THA.

We then asked whether certain common patterns of hip OA breed true[16] (Figure 3). The main patterns we examined were the direction of femoral head migration (e.g., superior, lateral, medial). As has been shown in previous community and hospital-based series, we found that axial and medial migration of the head were the least common patterns, were more common in women than in men, and were more commonly bilateral than unilateral. In addition, we classified the bony reaction dichotomously, as either hypertrophic or atrophic (illustrated in Figure 3), to provide a pattern of recognition of the amount of osteophytosis or bone attrition that was present. It is important to note, however, that about 30% of cases were indeterminate, i.e., could not be classified as either atrophic or hypertrophic.

In comparing the risks in siblings, we found that if the index case had atrophic OA, the likelihood of development of hip OA in siblings was much greater than that in siblings of index cases with hypertrophic OA. Also, atrophic OA in the index case was associated with a high risk of TJA. Thus, genetic studies in which phenotypes are based on joint replacement may be somewhat unrepresentative of OA in a general sense (i.e., they may under-represent hypertrophic OA). Interestingly, the pattern of femoral head migration or



- axial and medial patterns least common, female > male, bilateral
- 'atrophic' versus 'hypertrophic'

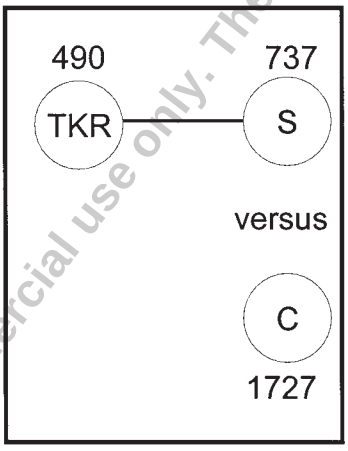
  OR for definite OA in a sibling = 2.05 (1.12-3.76)

  OR for THA in a sibling = 3.05 (1.53-6.07)
- migration and bone response not concordant within families

Figure 3. Patterns of hip OA. The top radiograph shows the 3 main patterns of femoral head migration. S: superior, A: axial, M: medial (see text). The lower radiograph shows the "atrophic" pattern of hip OA (marked bone attrition, paucity of osteophytes). OR: odds ratio, THA: total hip arthroplasty. Adapted from Lanyon, *et al*. Ann Rheum Dis 2004;63:259-63[16].

of atrophic/hypertrophic bony change was not concordant within families. Thus, the risk of acquiring OA is strongly familial, but the type of hip OA may relate as much, or more, to constitutional and environmental factors as it does to heredity.

Figure 4 summarizes a similar study performed in subjects with knee OA[17] (Table 1). Index cases were patients presenting for TKA. Siblings of these individuals were examined regardless of whether they reported knee pain, and the radiographic prevalence of knee OA in the siblings was compared with that in a community sample. After adjustment for risk factors, such as age, sex, Heberden's nodes, BMI, smoking, and meniscectomy, the results indicated an increase in the adjusted odds ratio in the siblings for the prevalence of OA in both the tibiofemoral and, albeit to a lesser extent, patellofemoral compartment. These data are



- increased aOR in siblings (age, sex, nodes, BMI, smoking, meniscectomy)

tibiofemoral compartment	
KL ≥ 2	2.5 (1.8-3.4)
KL 3-4	2.5 (1.7-3.7)
bil ≥ 2	2.0 (1.3-2.9)

patellofemoral compartment	
N ≥ 2 + OST ≥ 2	1.9 (1.4-2.6)
N ≥ 3 + OST ≥ 3	1.6 (1.1-2.4)
bil ≥ 2	1.8 (1.2-2.7)

- aRR (Poisson) 1.6 (1.4-2.0)

Figure 4. Knee OA sibling study. TKR: Total knee replacement; aOR: adjusted odds ratio, S: siblings of patients who had undergone total hip replacement, C: community sample, BMI: body mass index, aRR: adjusted relative risk, bil: bilateral (see text). KL: Kellgren-Lawrence grade, N: joint space narrowing, OST: osteophyte. Adapted from Neame, *et al*. Ann Rheum Dis 2004;(in press).

Table 1. Knee OA sibling study. Index cases (n = 490) were identified on the basis of total knee arthroplasty (TKA) and their siblings (n = 737) (S) were compared with a community sample of 1727 subjects (C). After adjustment for age, sex, Heberden's nodes, BMI, smoking and meniscectomy, the adjusted odds ratio (aOR) for radiographic OA was increased in the tibiofemoral and patellofemoral compartments of the knee. From Neame, *et al*. Thesis. Nottingham: Nottingham University; 2002.

Tibiofemoral Compartment		Patellofemoral Compartment	
OA Severity	aOR	OA Severity	aOR
KL ≥ 2	2.5 (1.8–3.4)	Narrowing ≥ 2 + osteophyte ≥ 2	1.9 (1.4–2.6)
KL 3–4	2.5 (1.7–3.7)	Narrowing ≥ 3 + osteophyte ≥ 3	1.6 (1.1–2.4)
Bilateral KL ≥ 2	2.0 (1.3–2.9)	Bilateral Narrowing ≥ 2 + osteophyte ≥ 2	1.8 (1.2–2.7)
aRR (Poisson) = 1.6 (1.4–2.0)			

KL: Kellgren-Lawrence grade of OA severity. aRR = adjusted relative risk.

consistent with those from the hip studies and indicate a strong genetic predisposition to radiographic knee OA.

Family studies. With respect to the third strategy, i.e., examining the distribution of OA within families, 2 major studies have been published to date: The Baltimore Longitudinal Study of Aging[18] examined nuclear families (defined as those having at least one parent and one offspring) in a population setting in which families were selected regardless of the presence of OA or self-reported joint pain. This, therefore, was a proper random sample of a community set of families, in which individuals underwent radiographs of the hand or knee or both. Kellgren-Lawrence scores indicated an increase in sibling correlations for OA at certain hand joints, but not at the knee. However, if scores for hand joints and knees were summed, the result indicated an increased risk of OA at several sites, i.e., polyarticular disease. Although this study failed to show a familial contribution to knee OA, it is interesting to consider how we should weight hand joints and knee joints in attempting to try to combine them to provide a polyarticular OA score.

The other important study examining the distribution of OA within families is the Framingham Study[19], which identified nuclear families in the community that were not necessarily selected according to their OA status, thus representing a random sample. Radiographs of hands and knees were obtained. A large number of these family members and their offspring have now reached the age at which a reasonable prevalence of OA can be expected — the mean age of the offspring is now 54 years. Some of the families were large, but the median number of offspring was 2.

Parent-offspring and sib-correlations were in the order of 0.12–0.30. Looking at the pattern of segregation through families, the best-fit model of inheritance was a Mendelian recessive, with an additional residual component that could be explained by either polygenic or environmental interactions. This is not the only model that may fit the data, but the results add to the evidence for a strong inheritable effect that explains the variance of OA in the population.

A third family study, currently in progress, is the very large population study being conducted in a suburb of Rotterdam, in which some 15,000 people have been recruited, regardless of symptom status[20]. One hundred eighteen subjects age 55–70 years were found to have multiple-site radiographic OA. The prevalence of generalized OA in the siblings of that group, based on the summed score of Kellgren-Lawrence grades for the joint sites examined, revealed very high heritability (0.78). Further, heritability was high also for intervertebral disc degeneration and hand joint OA alone, although this community sample did not show much of a genetic effect for either knee OA or hip OA. Whether the sample was underpowered in this respect or this reveals a real difference from the findings in the other family studies noted above is unclear.

Elsewhere in these proceedings Moskowitz discusses the exciting work his group is now performing to identify the specific genes that may underlie a familial predisposition to OA[21]. A genetic association is found mainly by linkage in sib-pair family studies. However, associations in case-control studies may be helpful in identifying areas of chromosomes that indicate an apparent association, or may lead to the search for more specific candidates.

Interestingly, genetic associations with OA appear to be different at different joint sites. As Dr. Moskowitz indicates, an apparently strong association of chromosome 2q with hand OA, defined chiefly as Heberden's nodes, has been noted. However, if hand OA is defined differently, in a different population setting, the association may be lost[22].

A number of problems exist with our current studies. First, unless an extremely strong single gene association exists, many studies are probably underpowered with respect to their ability to detect associations. A problem exists also with the use of different definitions of OA and different radiographic scoring systems, making comparisons between studies difficult. Although most of the candidate genes reported to date relate to structural components of the joint (e.g., cartilage or bone), it is worth noting that potentially relevant nonstructural molecules, such as insulin-like growth factor (IGF), are involved in much more general processes related to body health, and not only to structure of cartilage or bone. Thus, we may be surprised to find a much

more generic, system-wide, body-wide genetic association in OA than would exist if the association were only with a structural gene.

In looking for individual OA genes, if we examine families with a very unusual phenotype, e.g., presentation at a young age, with multiple joints involved and a very high percentage of siblings affected, we will be focusing on a mutation whose frequency in the population is rare, but which when present has a dynamic effect in producing the phenotype (about 100% expression). In such rare phenotypes "OA" will result from a monogenic condition that will have very little relevance to more common OA.

On the other hand, at the other end of the spectrum, i.e., in subjects with common OA, we may be dealing with multiple common polymorphisms, each of which has a very small attributable risk of causing the appearance of the phenotype unless many other, e.g., constitutional/environmental factors also are present in that individual. It seems increasingly likely that we will find ourselves looking for a few — or even multiple — common polymorphisms, rather than for rare mutations, to explain the observed strong familial risk of OA. Finally, when we identify the individual genes involved, we will probably have a relatively long list of genes relating to a variety of processes that may relate to the health of joint tissues, with a phenotype influenced by other risk factors. The next step will be gene–gene and gene–environment interaction studies that will be needed to enlarge our understanding of the manner in which the individual genes that are implicated in OA exert their effect. Understanding the genetic basis for OA will require the availability of large cohorts of extremely well characterized individuals with hip OA, knee OA, or multiple joint OA.

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