We report a study of 112 patients with primary anteromedial osteoarthritis of the knee and their families. Sibling risk was determined using randomly selected single siblings. Spouses were used as controls. The presence of symptomatic osteoarthritis was determined using an Oxford knee score of ≥29 supported by a Kellgren and Lawrence radiological score of II or greater.

Using Fisher’s exact test we found that there was a significant increased risk of anteromedial osteoarthritis (OA) relative to the control group (p = 0.031). The recurrence risk of anteromedial OA to siblings was 3.21 (95% confidence interval 1.12 to 9.27). These findings imply that genetic factors may play a major role in the development of anteromedial OA of the knee.

Anteromedial osteoarthritis (OA) is a distinct phenotype of osteoarthritis.1 The arthritic lesion is localised to the anteromedial quadrant of the tibiofemoral joint. Erosion of the cartilage within the medial compartment begins in the anterior half of the tibial plateau, with preservation of the cartilage in the posterior third. There is a corresponding lesion on the distal femoral condyle, and an intact anterior cruciate ligament (ACL). Previous studies have shown a genetic contribution to the aetiology of osteoarthritis of both hip2,3 and knee,4 in addition to other degenerative joint conditions.5,6 The relative contributions of genes and environment vary for different joints with OA.7 Unlike other patterns of joint wear, the consistent appearance of the lesion in the tibial plateau suggests that it is related to increased loading in this region and may, therefore, be a result of environmental factors. This study aimed to determine the sibling risk of anteromedial osteoarthritis of the knee.

Patients and Methods

From our computerised database of patients with primary anteromedial OA of the knee who were potentially available for the study. Of the 155 siblings (75 female, 80 male), eight refused to participate. The remaining 147 siblings (69 female, 78 male) were members of 112 families. The mean age of the probands was 68.1 years (41 to 90).

In order to reduce the risk of ascertainment bias, one sibling per family was randomly selected. Ethical approval was obtained for the study. This precluded radiological examination of symptom-free joints. The mean age of the siblings was 65.2 years (40 to 86), 52 were female and 60 were male. As in some previous studies,5,6 spouses of siblings were used as controls. Of the 90 controls 42 were female and 48 male. The mean age was 66.5 years (40 to 84).

Significant symptoms were defined as an Oxford knee score8 of ≥29 where a score of 0 indicated the most severe symptoms and a score of 48 had no symptoms whatsoever. Any siblings or spouses with such a score were asked to attend for anteroposterior (AP), lateral, standard skyline,9 and Rosenberg10 knee radiographs. For those patients who had previously undergone knee surgery their most recent pre-operative radiographs and radiology reports were obtained from their local hospital. Rosenberg10 views were not available for these patients. All radiographs were reviewed independently by two orthopaedic knee surgeons (SMMD and AJP) and graded according to the Kellgren and Lawrence classification.11 The Kappa value for interobserver agreement
for assessment of radiographs using this classification was 0.64. Siblings or spouses who had a Kellgren and Lawrence grade greater than II were considered to have OA. The pattern of disease was also defined (anteromedial, lateral, patellofemoral or tricompartmental).

Fisher exact tests as implemented in the software package STATA (StataCorp LP, College Station, Texas) version 7.0 were used to analyse the data in the contingency table. Statistical significance was defined as a p-value < 0.05. Risk estimates based on the presence of anteromedial OA in siblings and spouses were obtained using the following equation:

$$\lambda_s = \frac{\% \text{ siblings with anteromedial OA}}{\% \text{ controls with anteromedial OA}}$$

where $\lambda_s$ is the relative risk to siblings.

The result is given as a ratio with 95% confidence intervals (CI). This represents the increased risk that genetically-linked siblings of patients with anteromedial OA have when compared with non-genetically-linked controls.

**Results**

The sibling and control groups were seen to have similar age and gender distributions. The proportion of males did not differ significantly between siblings and controls (chi-squared test, $p = 0.3413$) and the mean ages were not significantly different. Of the 112 siblings and 90 controls, 20 (17.8%) and 4 (4.4%) respectively either had symptoms, or had previously undergone knee replacement (recurrence risk in siblings $= 4.41$, 95% CI 1.57 to 12.42, Fisher’s exact test, $p = 0.0018$).

In the symptomatic sibling group, three had previously had total knee replacements (TKRs), three had previously had UKRs and 14 had had no previous knee surgery.

Radiographs (including pre-operative radiographs) of symptomatic siblings as defined by the Oxford knee score revealed that 16 had a medial pattern of disease, three had tricompartmental disease and one had radiological changes less than Kellgren and Lawrence grade II.

In the control group one spouse had previously had a TKR, and one a UKR. Radiographs revealed that both had a medial pattern of disease.

A total of 16 of the 112 (4.3%) siblings and four of the 90 (4.4%) controls were defined as having anteromedial OA.

The relative risk to siblings was calculated as 3.21 (95% CI 1.12 to 9.28, Fisher’s exact test, $p = 0.0308$). The siblings who did not fit the defined Kellgren Lawrence criteria have been excluded from this calculation.

**Discussion**

This is the first study that has investigated genetic factors in a specific sub-group of OA of the knee. Evidence already exists which shows that there is a significant genetic component to the development of primary OA. In a twin study by Zhai et al, medial compartment OA is shown to have a genetic component with a heritability of 69% for osteophytes and 80% for joint space narrowing. However, they did not look at more advanced disease. Our results demonstrate that, for a subgroup with anteromedial OA, the disease is much more common in siblings than in a control group of similar age and gender distribution. The results are similar to previous studies of generalised OA.

An alternative possibility is that siblings share a common environment. However, we reduced the likelihood of this by using spouses as controls. The effect is to compare a group who were more likely to have shared similar environmental risk factors as in earlier recurrence risk studies. Gender difference variations are reduced by having matched male/female distributions within the sibling and control group.

The sample size within our group was smaller than previous studies. We used single sibling proband pairs to reduce the risk of ascertainment bias, which, as a consequence, decreased the number of siblings available for the study. However, even with the smaller sample size, the recurrence risk to siblings is still significantly greater than one.

We used the Kellgren and Lawrence classification system which has been shown to have a high reliability for knee OA and strong interobserver agreement. Radiographs were reviewed by two orthopaedic surgeons (SMMD, AJP) who were unaware of the patient details at the time of surgery.

We used strict criteria for defining the presence of anteromedial OA in addition to preservation of the lateral compartment. Patients who had tricompartmental disease were excluded.

Since anteromedial OA was first described by White et al, it’s aetiology has been debatable. The preservation of cartilage within the other compartments of the knee has led to the assumption that it is a more mechanical pattern of disease. This study demonstrates that genetic factors are significant in its aetiology.

A further study is required to determine whether the genes in question are influencing the quality of articular cartilage and subchondral bone, or the varus alignment of the knee or the pattern of gait.

By improving our understanding of the aetiology of this common subgroup of OA of the knee, investigators may be able to identify early disease and either prevent its progression or treat the lesion without the need for knee replacement surgery.

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**References**