Primary Osteoarthritis of the Hip in Monozygotic and Dizygotic Male Twins

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Population and total hip replacement surveys show that primary osteoarthritis of the hip is uncommon in African Americans and rare in Asians, suggesting a genetic basis for this disease. We studied genetic influences on primary osteoarthritis of the hip by estimating monozygotic (MZ) and dizygotic (DZ) twin correlations using a two-stage data collection. A total of 6419 male veteran twins of the NAS-NRC Twin Registry, born between 1917 and 1927, were contacted by telephone (first stage). Telephone interview determined that 2% reported a total hip replacement for arthritis rather than fracture. X-rays of twin pairs in which one twin had undergone total hip replacement were sought and reviewed (second stage), and concordance for primary arthritis was determined based on x-ray diagnosis. Heritability of primary osteoarthritis, Kellgren & Lawrence Grade II and higher, was estimated using a covariance structure analysis for 2-stage data. The best-fitting model included only components for additive genetics and for unique environment. Additive genetics accounted for 53% (95% confidence interval 30–72%) in the liability for self reported hip replacement surgery and unique environment for the remaining 47% (95% confidence interval 28–70%). Additive genetics accounted for 61% (95% confidence interval 18-86%) of the variance in liability for x-ray determined primary osteoarthritis with unique environment accounting for the remaining 39%. These data establish a genetic influence on primary osteoarthritis of the hip in male twins and suggest that further work is indicated to isolate the genes responsible for this disease.

Primary osteoarthritis (POA) of the hip occurs in 4% of the White population (Danielson & Lindberg, 1997; Lawrence et al., 1989) and accounts for two-thirds of the 140,000 total hip replacements done annually in the United States. In contrast, primary osteoarthritis of the hip is rare in Jamaicans (Bremmer et al., 1968), in native Africans (Solomon et al., 1975), Indians (Mukhopadhaya & Barooah, 1967), and Asians (Hoaglund et al., 1995; Hoaglund et al., 1973; Lau et al., 1995; Nakamura et al., 1989). In the United States total hip replacement (THR) for POA of the hip is uncommon in African Americans (Hoaglund et al., 1985), and rare in Asians (Oishi et al., 1998) living in the same environment as Whites suggesting that genetic factors are involved in this disease.

Family studies in England and Sweden have also suggested a genetic basis but could not rule out familial clustering from environmental causes (Chitnavis et al., 1997; Lindberg, 1986; Lanyon et al., 2000). Other studies have found environmental risk factors such as the occupation of farming (Axmacher & Lindberg, 1993; Thelin, 1990), jobs requiring heavy lifting (Croft et al., 1992), and elite sports activity (Heliövaara et al., 1993; Vingård et al., 1991). POA of the hip is a separate disease from that occurring in other joints (Cushnaghan & Dieppe, 1991), and patients with hip osteoarthritis do not have knee osteoarthritis and vice versa. A recent study of British female twin pairs showed that osteoarthritis of the knee and hand were subject to genetic influence (Spector et al., 1996), and a subsequent study showed a significant heritability for radiographic hip osteoarthritis (MacGregor et al., 2000).

Materials and Methods

Subjects

Our study population come from the National Academy of Sciences-National Research Council Twin Registry, a population-based twin registry composed of white male twins born in the years 1917 to 1927 (inclusive) who served in the United States military (Jablon et al., 1967). The registry was assembled from some 54,000 birth certificates matched against the Department of Veteran Affairs records to ascertain Veteran status, and it is thought to represent 93% of eligible male-male twin births occurring during this period. A total of 15,924 veteran twin pairs were eventually identified. Zygosity was ascertained using questionnaire, blood type, anthropometric data, eye and hair color, fingerprints, and serological results. Validity studies suggested that the questionnaire data alone provided a correct diagnosis of zygosity in 95% of twin pairs (Braun et al., 1994). The study population consisted of the 6419 living male twins whose location could be determined at the time of the telephone survey.

Data Collection

A telephone survey was conducted by the Duke University Dementia Study Group under the direction of Dr. John C. S. Breitner. Although the survey was directed primarily

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at neurodegenerative disease, two questions related to hip pain and total hip replacements were asked of each twin: 1) Have you ever had a problem with pain in one or both hips, which may be due to arthritis? and 2) Have you ever had an operation for total hip replacement for arthritis but not for hip fracture? One hundred and twenty-eight of the 6419 twins (2%) reported a total hip replacement.

Those twin pairs in which at least one twin had a total hip replacement were contacted by mail and asked to provide the name and address of their doctor and hospital to allow recovery of their x-rays and medical records. Information was requested by written questionnaires about the age and onset of hip symptoms, the age and diagnosis for total hip replacement, history of childhood hip disease, major hip injuries, prednisone ingestion, and history of total hip replacement in other siblings. Co-twins were sent similar questionnaires which also requested specific information about hip pain (pain in the groin, trochaneteric region, or lateral buttock lasting longer than 2 months), difficulty getting up from a chair, or limp with walking.

After receiving completed questionnaires and medical release forms, orthopedic surgeons and hospitals were contacted to provide pre-operative pelvic x-rays and appropriate medical record information. Follow-up telephone discussions were done with patients to verify and complete missing data.

All twins not having a total hip replacement with or without symptoms of pain about the hip were invited to take a single pelvic x-ray at our expense. Pre-operative pelvic x-rays of total hip replacement patients and x-rays of unoperated patients were analyzed independently and the diagnosis agreed upon conjointly by an orthopedic surgeon (FTH) and a musculoskeletal radiologist (LSS) without knowledge of zygosity or matching co-twin. When there was disagreement, x-rays were sent to three expert reviewers and the diagnosis was made by consensus. Simple kappa statistics for interrater reliability for diagnosis where both reviewers reported definite hip disease was 0.745 for the right hip and 0.846 for the left hip.

Standard radiographic criteria were used for the diagnosis for developmental dysplasia of the hip, rheumatoid arthritis, inflammatory arthritis, osteonecrosis, posttraumatic osteoarthritis. The diagnosis of POA was made by exclusion of other causes of hip disease using Grade II or greater of Kellgren and Lawrence's criteria (Kellgren & Lawrence, 1957). Grade II requires both osteophyte and minimal but definite joint space narrowing. Grades III and IV have moderate and severe changes of osteoarthritis.

Analysis

Heritability was estimated using a covariance structure analysis conducted using Mx software package (Neale, 1997). For this analysis, the two outcome traits (self-reported data on hip surgery from the telephone survey and primary osteoarthritis POA of the hip determined by x-ray) were analyzed jointly in a multivariate model using a Cholesky decomposition (Neale & Cardon, 1992). The self-reported data were treated as screening data, since only twins who self-reported hip surgery (and their co-twins) were subsequently asked to provide x-rays.

Results

There were 6419 respondents to the telephone surveys. Excluding two missing responses, the self-reported rate of hip surgery was 2.0% (128/6417). There were 2562 twin pairs in the survey, and after excluding two pairs with incomplete responses and 199 pairs of unknown zygosity, we were left with 1224 informative MZ pairs, and 1137 DZ pairs. Overall response rates to the telephone survey were 85.2% for MZ twin pairs and 81.7% for DZ twin pairs.

Of the 128 twins who reported total hip replacement surgery, 25 singleton twins were not contacted, and an additional 11 twins could not be contacted. X-ray diagnosis was available in 61 of the remaining 92 twins reporting a total hip replacement. Pre-operative X-rays revealed that the operation had been done for osteonecrosis (1 patient), rheumatoid arthritis (1 patient), inflammatory arthritis (1 patient), fracture (3 patients), and developmental dysplasia of the hip (DDH) (3 patients). Radiographic POA of the hip was diagnosed in 85% (52/61) of the cases.

Of the unoperated co-twins, 49 reported no hip pain symptoms, and of these, 26 agreed to have x-rays taken. Among the 26, 4 had osteoarthritis (19%) and 1 had calcium pyrophosphate deposition disease (CPDD). Another 19 co-twins reported symptoms of hip pain. Of these, 17 patients had hip radiographs. Eleven were normal, and 6 had features of POA. Two symptomatic patients did not agree to an x-ray. Finally, 5 twins of unknown symptomatology had x-rays, 4 of whom had POA. Therefore, 30% (14 of 48 non total hip replacement twins with x-rays) had radiographically demonstrated POA.

The covariance structure analysis determined that the best fitting model included two components, one for additive genetics (A) and one for unique environment (E) (i.e., common environment was not a statistically significant factor). Table 1 shows the results for the best fitting, AE model. Additive genetics accounted for 53% (95% confidence interval 30–72%) of the variance in liability for

Table 1

Results of Covariance Structure Analysis Model Fitting

Trait	Additive Genetic Component (95% confidence interval)	Unique Environmental Component (95% confidence interval)
Total hip replacement surgery	53.4% (30–72%)	46.6% (28–70%)
X-ray determined POA	60.9% (18–86%)	39.1% (14–82%)
Bivariate Correlation	0.76 (0.10–1.00)	0.57 (0.26–0.84)

self-reported hip replacement surgery, and unique environment accounted for the remaining 47% (95% confidence interval 28–70%) variance. Additive genetics accounted for 61% (95% confidence interval 18–86%) of the variance in liability for x-ray determined POA, with unique environment accounting for the remaining 39% (95% confidence interval 14–82%) of variance.

The genetic correlation measures the extent to which genetic influences of one trait overlap those of the other trait. The value of 0.76 (95% confidence interval 0.10-1.00) indicates a good deal of overlap between the genetic influences on self-reported hip surgery and x-ray diagnosed POA. Thus to a large extent, the same genes are influencing both traits. The correlation between the unique environment components for two traits, 0.57 (95% confidence interval 0.26–0.84), is moderately high, showing that the unique environmental factors influencing self-reported hip surgery overlap somewhat those influencing x-ray diagnosed POA.

Discussion

Our data represent one of the few twin studies of radiographic hip osteoarthritis in male twins. Although Kirk et al. (2002) have recently published work on osteoarthritis in male and female twins, they could not do multivariate structural equation modeling for male twins, due to small numbers of affected males at the various osteoarthritis sites. MacGregor et al. (2000) reported similar findings to ours in their study of female twins over age 40, finding a heritability of OA (Kellgren & Lawrence grade II or higher) of 58%. Their study involved twins with an average age of 53 years, roughly 2 decades younger than the twins in our sample. Overall, about 1% the female twins in the MacGregor et al. study had osteoarthritis of the hip with a Kellgren and Lawrence (K&L) grade III or grade IV, compared to roughly 2% of our male twins. The usual indications for total hip replacement surgery are a K & L grade III or higher. Because all of our twins who were asked to provide x-rays had reported total hip replacement surgery, they were virtually all K & L grade III or higher.

Although generalized osteoarthritis has been shown to have a genetic basis, it is not reasonable to consider OA as a single disease and group different joints together in epidemiological and linkage studies. Osteoarthritis of the hip and knee are separate and independent; for example, the incidence of osteoarthritis of the hip is 4% and that of the knee at least 15%. For this reason, we limited our study to osteoarthritis of the hip. Although Kujala et al. (1999) studied osteoarthritis in male and female twins in the Finnish Twins Registry, their findings were based on self-reported physician-diagnoses, and they did not provide separate estimates of heritability for hip osteoarthritis. Interestingly, their analysis of non-joint-specific osteoarthritis in men found a significant genetic effect in female but not in male twins, although there was a significant influence of common environment in male twins. While we did not find a statistically significant influence for common environment for THR and POA, it should be noted that the classical twins study has limited power to differentiate

between additive genetic and common environmental effects (Neale et al., 1994).

Linkage studies also provide evidence that genetic susceptibility to osteoarthritis may vary by joint group and may also depend on sex (Loughlin, 2002). For example, linkage studies have shown evidence of linkage to markers on chromosome 11q for female sib pairs, but not for males (Chapman et al., 1999), while evidence of linkage to chromosome 2q was stronger in males with osteoarthritis of the hip than in females with osteoarthritis of the hip (Loughlin et al., 2000). Another study identified linkage between the type IX collagen gene, COL9A1 (6q12-q13), for females with osteoarthritis of the hip, but not for males (Mustafa et al., 2000). Such differences between study results highlight the complex nature of genetic susceptibility to osteoarthritis.

Radiographic studies of the hip compared with other joints have the advantage that specific causes of hip disease such as osteonecrosis, trauma, and hip dysplasia can be separated from POA. Some authors consider the majority of POA to be caused by predisposing anatomical abnormalities (Murray, 1965; Solomon et al., 1975; Stulberg & Harris, 1974). It is possible that some patients diagnosed in this study as POA had preexisting anatomical abnormalities (Goodman et al., 1997) or that there is some as yet unrecognized subtle anatomical difference accounting for the majority of them. Since x-rays were viewed independently, and an agreed conjoint diagnosis made without knowledge of zygosity or matching twin, this should eliminate bias in the measurement of heritability.

Regarding other potential biases, we note that response rates to the survey were similar for MZ (85.2%) and DZ (81.7%) twin pairs. The average age of MZ twins at time of survey (73.32 years, standard error = 0.06) was not significantly than that of DZ twins (73.41, standard error = 0.06). We did not collect contemporaneous data on weight, but self-reported weight from a 1985 survey was nearly the same for MZ twins (176.49 pounds, standard error = 0.39) as for DZ twins (177.45 pounds, standard error = 0.38). Because the age range of our twin sample was relatively narrow and because we did not have contemporaneous data on weight, we did not include age or weight in our structural equation models.

Our data provide evidence for a number of general observations. First, genetics do play a significant role in osteoarthritis of the hip in men, as has been seen in studies of women. Further, because we collected our data in two stages — telephone screening followed by examination of radiographic evidence — we can compare and contrast the results of these two methods. Although a radiographic definition of POA is much to be preferred, heritability estimates for liability to self-reported hip surgery and for liability to radiographically diagnosed primary osteoarthritis of the hip are remarkably similar: 53% and 61%, respectively. The high genetic correlation of 0.76 further indicates that the same genetic influences underlie both traits. Finally, we note that by screening a population-based twin registry and analyzing twins regardless of their treatment status, we have avoided the

possible bias that might have come about by advertising to attract probands.

In summary, in this group of men who were roughly 70–80 years of age at time of study, we found that genetics had a significant influence on the development of primary osteoarthritis of the hip, accounting for an estimated 61% of the variation in liability to POA diagnosed by x-ray. Although further work to find and isolate the genes responsible for POA may be difficult, our results suggest that such an effort could be justified.

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Appendix A

113 x-rays were available for evaluation. Of these, 33 were normal. In those with hip disease, the x-ray diagnosis was primary osteoarthritis in 66, post-traumatic arthritis in 3, developmental dysphasia of the hip in 3, rheumatoid arthritis in 1, CPDD in 1, inflammatory hip disease in 1. In 4 patients, only post-operative x-rays were available the total hip replacement showing and a normal opposite hip. Physician and hospital information was available for 14 patients where x-rays were unavailable or had been destroyed. The physician diagnosis was osteoarthritis in 9, rheumatoid arthritis in 3, hemochromatosis in 1, Legg-Calve-Perthes disease in 1, and Paget's disease in 1.