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A Heritable Predisposition to Osteoarthritis of the Hip

Christopher E. Pelt, MD [a], Jill A. Erickson, PA-C [a], Christopher L. Peters, MD [a], Mike B. Anderson, MSc [a], Lisa Cannon-Albright, PhD [b,c]

[a] Department of Orthopaedics, University of Utah School of Medicine, Salt Lake City, Utah
[b] Division of Genetic Epidemiology, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah
[c] George E. Wahlen Department of Veterans Affairs Medical Center, Salt Lake City, Utah

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ABSTRACT

Using THA as a proxy for underlying osteoarthritis, we describe population-based familial clustering of osteoarthritis of the hip. The GIF test for excess relatedness on 1049 patients that underwent THA (and do not have a diagnostic code for other conditions leading to THA) showed excess relatedness ($P < 0.001$). Even when close relationships were ignored (closer than third-degree relationships), excess relatedness was observed ($P = 0.020$). Relative risk was elevated in first-degree (RR 2.59; 95% CI 1.84–3.53, $P = 2.0e^{-7}$), second-degree (RR 1.66; 95% CI 1.11–2.39; $P = 0.0075$) and third-degree relatives (RR 1.46; 95% CI 1.17–1.81; $P = 5.7e^{-4}$). Excess relatedness of individuals who had undergone THA for osteoarthritis and elevated risks to both near and distant relatives were observed.

Hip osteoarthritis remains among the leading causes of global disability [1]. An aging population with higher life expectancy and functional demands will continue to increase the demand for total hip arthroplasty (THA) [2]. Attempts to further understand the risks and interventions to prevent the need for THA due to the progression of hip osteoarthritis are warranted. The etiology of hip osteoarthritis, and therefore the need to undergo THA, is likely multifactorial. Among many identified risks to the development of hip osteoarthritis, a genetic predisposition has been described [3–10].

Although familial aggregation, primarily in sibling studies of THA [3], and potential genetic polymorphisms of structural hip abnormalities and hip arthritis have been suggested [9,11], we are aware that no study that has evaluated the familial clustering of osteoarthritis leading to THA on a population-based, multigenerational level in the United States. The Utah Population Database allows the combination of a computerized genealogy of the Utah founding pioneers and their descendants with disease diagnosis data [12]. The Utah genealogy database has been linked to the University of Utah Health Sciences Center data warehouse. The resultant information is a unique and invaluable resource that has been used to evaluate familial clustering in other disease processes [13–16].

The purpose of this study was to define the familial clustering observed among individuals with hip osteoarthritis (using THA and absence of other conditions leading to THA as a proxy for underlying osteoarthritis). We tested the hypothesis of a heritable predisposition to severe osteoarthritis leading to THA using two well-established methods: the estimation of relative risks in relatives and the Genealogical Index of Familiality.

Data and Methods

Both the University of Utah institutional review board and the oversight body for the Utah Population Database approved this study. No patient identifiers were used in this study, and analysis of all genetic relationships between affected individuals was non-identifiable.

The Utah Population Database

The Utah Population Data Base, or UPDB, is a population-based resource including most vital statistics data for Utah, and also including the computerized genealogy of the Utah pioneers from the mid 1800s and their descendants to the current day [12,17]. This genealogy data have been linked to various health-related datasets in Utah including electronic medical data for patients of the University of Utah Health Sciences Center (UUHSC) since 1994. The UPDB includes 1.3 million individuals with genealogy data for parents, all four grandparents, and at least 6 of their 8 great grandparents. These individuals, with at least 12 of their 14 immediate ancestors, are used for the analyses presented. Approximately 370,000 of these individuals have been a patient at UUHSC and have medical data available.

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Reprint requests: Christopher Pelt MD, University of Utah, Department of Orthopaedic Surgery, 590 Wakara Way, Salt Lake City, Utah 84106.

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University of Utah Health Sciences Center (UUHSC) Data

Data can be queried based on International Classification of Disease Revision 9 (ICD9) diagnosis codes or Current Procedural Terminology Revision 4 (CPT4) procedure codes. All patients who had undergone THA for osteoarthritis (cases) were identified by presence of CPT-4 procedural codes (27091, 27130, 27134, 27125, 27090, 27137, 27138), or ICD9 codes (996.46 or 996.66), indicative of THA surgery reported within the UUHSC database. Due to significant variability in coding for diagnoses leading to the need to undergo THA, we primarily relied on the procedural codes for THA, which show less variation in coding consistency. In an effort to further optimize the ability of the THA procedural code to identify patients undergoing THA for osteoarthritis of the hip as opposed to other underlying hip disorders that could lead to THA, patients with co-documented ICD9 codes for other common hip disorders that would also lead to THA were excluded. These included diagnosis of rheumatoid arthritis, post-traumatic arthritis, avascular necrosis, and childhood hip diseases, and resulted in 158 patients being removed from the analysis. Ultimately, the query identified 1049 patients that underwent THA and who had at least 12 of their 14 immediate ancestors spanning 3 generations in the database; these were termed osteoarthritis cases; 877 (84%) of these individuals also had a hospital record that included a diagnosis of osteoarthritis (ICD9 715+).

Controls for Genetic Analyses of Familial Clustering

Both of the two different analyses of familial clustering require comparison of observed results with the expected results for the Utah population; thus all analyses require the identification and analysis of appropriately matched controls. Controls for all analyses were selected from the approximately 370,000 UUHSC patients with at least 12 of their 14 immediate ancestors available in the database. To allow appropriate matching for characteristics that may influence the quality and quantity of genealogical data or record-linking success, multiple different cohorts for these characteristics were created for all UUHSC patients in the UPDB. All individuals were assigned to a specific cohort on the basis of gender, 5-year birth-year range, and birth state (Utah or not), and birth county (urban or rural). Two different statistical analyses were performed on all genetic relationships represented between all patients who had undergone THA for osteoarthritis: the estimation of relative risks in relatives, and the Genealogical Index of Familiality test for excess relatedness.

Relative Risks (RR) in Relatives

Estimation of RRs for a phenotype among the relatives of affected individuals provides a traditional test for evidence of a genetic contribution to disease. Typically, RRs are estimated in first-degree relatives only, as this information is easily available for most affected individuals. However, although excess risk in first-degree relatives might indicate evidence of a genetic contribution, it could also simply indicate shared environment or exposure. Conversely, excess risks in second and third-degree relatives strongly support a genetic contribution to disease, given the measurable genetic sharing in these more distant relatives and the relative absence of shared household effects. RRs in first-degree relatives were estimated by counting the number of affected individuals among all first-degree relatives of patients who were UUHSC patients (without duplication) and comparing this to the expected number of affected individuals among the first-degree relatives of cases who were UUHSC patients; similar estimation was used for second and third-degree relative risks. The expected number of affected individuals requires calculation of the rate of osteoarthritis leading to THA in all UUHSC patients with genealogy data. We calculated cohort-specific rates by dividing the number of cases per cohort by the total number of UUHSC patients per cohort. To estimate the expected number of affected relatives, the count of relatives per cohort who are UUHSC patients is multiplied by the overall UUHSC rate of osteoarthritis leading to THA for that cohort, and then summed over all cohorts. The RR for osteoarthritis leading to THA among the first-degree relatives of cases is estimated as the observed number of cases divided by the expected number of affected patients. For each degree of relative, the significance of the alternative hypothesis RR ≥ 1.0 is calculated as a Fisher exact test and 95% confidence intervals are defined as described by Agresti [18].

Genealogical Index of Familiality (GIF)

The GIF analysis performs a test of the alternative hypothesis of no excess familial clustering (or pairwise relatedness) among all individuals with the phenotype of interest. In this test, the average relatedness of the set of patients with osteoarthritis leading to THA is compared to the expected relatedness of a similar set of individuals from the Utah population (using 1000 sets of matched hospital controls with genealogy data. The average relatedness of the patients with osteoarthritis leading to THA was calculated by measuring the pairwise genetic distance between all pairs of patients. The pairwise genetic distance is estimated using the Malécot coefficient of kinship, or the probability that the two individuals share the same allele from a common ancestor at a given locus [19]. The same measure of average pairwise relatedness is calculated for all possible pairs among a set of randomly selected, matched UUHSC controls; this process is repeated 1000 times, and the significance is measured empirically as the number of times the control relatedness exceeded the patient relatedness. The overall GIF statistic tests for excess relationships between pairs of patients versus pairs of controls, considering all relationships; the distant GIF (dGIF) test statistic is calculated similarly, but excludes relationships closer than third degree, and therefore provides a strong test for a genetic contribution to a phenotype, by ignoring close relationships among which shared lifestyle and risk factors would be more likely.

The GIF statistic is the sum of the mean relatedness across all pairwise genetic relationships. We can display the contribution to the GIF statistic by the genetic distance of the pairs. Genetic distance of 1 represents parent/offspring, 2 represents siblings, 3 represents avunculars, 4 represents first cousins, and so forth.

High-Risk Pedigrees

The identification of high-risk pedigrees (those with a statistical excess of patients with osteoarthritis leading to THA) uses a similar method to that described for RRs above. The ancestors of all cases are analyzed to identify patients with osteoarthritis leading to THA that descended from a common ancestor or ancestral pair. The number of UUHSC patients among all descendants of each set of ancestors is counted by cohort; the rates for osteoarthritis leading to THA are multiplied by the number of UUHSC patients in each cohort. RR for a significant excess = (number of observed cases/number of expected cases). Pedigrees with a $P < 0.05$ for RR > 1.0 are considered to be high-risk pedigrees.

Results

Relative Risks (RR) in Relatives

The estimated RRs for osteoarthritis in first-degree, second-degree, and third-degree relatives of patients with osteoarthritis are shown in Table 1. Significantly elevated risks for THA due to osteoarthritis are observed in first, second, and third-degree relatives of osteoarthritic patients. These results strongly support a genetic contribution for a predisposition to osteoarthritis leading to the necessity for THA.