Age, Sex, and the Familial Risk of Rheumatoid Arthritis

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The familial aggregation of rheumatoid arthritis was examined to determine factors modifying the risk of rheumatoid arthritis in first degree relatives of 165 cases ascertained from January 1, 1987, through March 31, 1987, using the Saint Margaret Memorial Hospital Rheumatoid Arthritis Registry, Pittsburgh, Pennsylvania, without regard to previous information concerning the occurrence of rheumatoid arthritis among their family members. The reported affection status of first degree relatives, verified through a structured clinical evaluation, revealed a false-positive reporting rate for family members of 61%. In contrast, there were no false-negative cases detected. There were no differences in average family size or total number of years at risk between 135 simplex and 30 multiplex families; however, aggregation analysis revealed that only 18 of 30 confirmed multiplex families had significant excess risk of rheumatoid arthritis. Significant differences were found when probands from multiplex families were compared with those from simplex families with regard to female to male ratio for probands (1:1 in multiplex families vs. 3:1 in simplex families) and average age of onset for probands (41 years in multiplex families vs. 48 years in simplex families). The familial risk for rheumatoid arthritis was similar in parents (4.2%) and siblings (4.6%) and lowest for children (0.7%) of probands. The authors assert that the affection status of first degree relatives of patients with rheumatoid arthritis is often falsely reported as positive. The familiality of rheumatoid arthritis may be more accurately related to the sex and age at onset of the affected family member. Am J Epidemiol 1996;144:15-24.

Several studies indicate that host factors (e.g., age and sex), environmental factors (e.g., Epstein-Barr virus infection), and genetic factors (e.g., genes in the human lymphocyte antigen region) may all play a role in the etiology and pathogenesis of rheumatoid arthritis (1-5). Neither the exact nor the relative roles of these factors and how they may interact with regard to etiology are known, however. Clinicians and researchers have frequently noted the familial clustering of rheumatoid arthritis, which suggests genetic and/or common, shared, environmental determinants. Additional evidence for a genetic component comes from the observation of an increased prevalence of rheumatoid arthritis in some isolated populations (e.g., the Chippewa Indians) (6). Furthermore, case-control studies have suggested a strong association between rheumatoid arthritis and human lymphocyte antigen class II genes. In particular, the pentapeptide sequence QKRAA (QRRAA), located in the third hypervariable region of the DRB1 gene, has been postulated to be a disease susceptibility epitope (7).

Nevertheless, the results of previous studies on the familial aggregation of rheumatoid arthritis have been conflicting. A recent review suggested no more than a slightly increased risk of rheumatoid arthritis among first degree relatives of probands and only a minimal genetic contribution (1). A study by Del Junco et al. (8) reported weak familial clustering as well as the possibility of disease heterogeneity based on the proband's age at onset of rheumatoid arthritis. The possibility of a large residual of sporadic cases was also raised. Twin studies (9-12) have shown a greater concordance of rheumatoid arthritis among monozygotic twins as compared with dizygotic twins and clearly suggest a genetic component to the risk of rheumatoid arthritis. Although an early study (10) noted a concordance rate of 30 percent among
monzygotic twins versus 9 percent among dizygotic twins, more recent twin studies have reported much lower rates: 12.5 percent versus 3.5 percent in a Finnish study (9) and 15.4 percent versus 3.6 percent in a study from the United Kingdom (11).

To better quantify the risk of rheumatoid arthritis among first degree relatives of probands, we collected reported family history of rheumatoid arthritis in a consecutive series of patients with rheumatoid arthritis ascertained without regard to previous information concerning the occurrence of the disorder among their family members. A structured clinical evaluation was performed to verify the reported affection status of probands and their family members. Because rheumatoid arthritis is a common, prevalent disorder, a test of familial aggregation was performed to confirm that familial aggregation was not due to chance and to identify these families and their characteristics demonstrating excess risk for rheumatoid arthritis. The characteristics of these families were then compared with those of families that did not demonstrate excess risk.

**MATERIALS AND METHODS**

Probands were identified from Saint Margaret Memorial Hospital Rheumatoid Arthritis Registry, which was established to provide clinical and epidemiologic investigators with a convenient index of information about all patients hospitalized with a primary or secondary diagnosis of rheumatoid arthritis (ICD-9 code 714.0, 714.1, or 714.2). The data, abstracted from each hospitalization record, contain clinical and demographic information on more than 2,000 individuals with rheumatoid arthritis discharged during the 3-year period January 1986 through December 1988. Saint Margaret Memorial Hospital, located in Pittsburgh, Pennsylvania, is a 267-bed community hospital with a strong rheumatologic-orthopedic focus. During the time of the study, patients with rheumatoid arthritis were routinely admitted to one of two 30-bed rehabilitation units for treatment of a flare-up of their disease. Previous studies have shown that the catchment area for the registry consists of Allegheny County, Pennsylvania (approximately two thirds of the patients), the surrounding nine-county southwestern Pennsylvania area (approximately one third), and parts of nearby Ohio and West Virginia (less than 5 percent) (13). A family history survey questionnaire was sent to 292 patients in the Saint Margaret Memorial Hospital Rheumatoid Arthritis Registry; these were consecutive patients discharged from the hospital during the period January 1, 1987, through March 31, 1987. The family history questionnaire was a modification of a previous version developed by Dr. Marc Hochberg, University of Maryland (used with the author's permission). Of the 292 patients, 254 (87 percent) responded. Seven patients were later excluded due to their misclassification (i.e., they did not have rheumatoid arthritis after chart review). The study was approved by the appropriate institutional review boards, and study subjects gave informed consent.

To assure accurate clinical verification of the reported affection status, a detailed standardized clinical evaluation was performed for all available individuals in the reported multiplex families and a randomly selected subset of the reported simplex families. The clinical evaluation included ascertaining historical information and performing a physical examination for any past or present history of arthritis, rheumatoid nodules, joint deformities, or comorbid disorders. Individuals were questioned regarding any signs or symptoms that might have suggested the presence of other rheumatic disease (e.g., systemic lupus erythematosus), and physical examination was performed to ascertain the presence of joint tenderness, joint swelling, joint deformity, or rheumatoid nodules. All histories and physical examinations were performed by two experienced clinicians (a board-certified rheumatologist [C. K. K.] and a clinical nurse [C. V.] with 9 years of experience in rheumatology and orthopedics). The first 50 individuals were examined by both clinicians in an effort to standardize the examinations. In general, families underwent clinical evaluation with both clinicians present, and the rheumatologist was available to review the examination if questions arose. For any family member who was suspected of having active or inactive rheumatoid arthritis, the individual's private physician was contacted to obtain corroborating evidence from inpatient and/or outpatient records and radiographs. Clinical data gathered from these records included the presence or absence of serum rheumatoid factor, antinuclear antibody, anemia, leukopenia, thrombocytopenia, proteinuria, radiographic evidence of erosions, any extraarticular manifestations, any previous biopsies, and past treatment with disease-modifying drugs. In addition, information on signs and symptoms related to other types of arthritis or connective tissue diseases was also collected to minimize the misdiagnosis of rheumatoid arthritis among these individuals. After detailed clinical evaluation, each individual family member was categorized (by C. K. K.) as being affected or nonaffected based on the American College of Rheumatology revised classification criteria for rheumatoid arthritis (14). In addition, individuals with current monarticular arthritis or asymmetric polyarthritis who fulfilled 1958 American Rheumatism Association revised clas-
sification criteria for probable rheumatoid arthritis were considered as having an intermediate status between being definitely affected or nonaffected.

Of the 247 families eligible for participation in this study, 150 were reported as simplex (i.e., only the proband was reported as affected), 73 as first degree multiplex (i.e., proband and at least one other first degree relative was reported as affected), and 24 as second degree multiplex (i.e., the proband and a second degree, but not a first degree, relative was reported as affected).

A total of 74 families (49 reported multiplex and 25 reported simplex) underwent clinical evaluation. All 73 families that were reported as first degree multiplex and a convenience sample of 25 reported simplex families were invited to undergo clinical evaluation to confirm affection status in family members. After clinical evaluation, 30 of 73 reported multiplex families were confirmed as being truly multiplex, and 19 of 73 were recategorized as simplex families inasmuch as the reported affected family members were found not to have rheumatoid arthritis (i.e., they were false-positive reports of rheumatoid arthritis). In 17 of the multiplex families, the proband and/or family members refused additional evaluation to verify the reported affection status after completing the initial family history questionnaire. In seven other multiplex families, the proband died after completing the initial family history questionnaire, and the family was thus lost to follow-up. All of the reported simplex families that underwent clinical evaluation were confirmed as being truly simplex. There was no difference in proband sex or age at onset between those families that underwent clinical evaluation and the 28 that refused (17 reported multiplex and 11 reported simplex probands).

During the course of the clinical evaluation of probands and their families, it became clear that probands often had very limited information about the affection status of second or third degree relatives, and information about second or third degree relatives was not uniformly ascertained from the probands. Therefore, all of our subsequent analyses focused only on first degree relatives. As a result, the 24 second degree multiplex families were trimmed to include only first degree relatives, and they were reclassified as simplex. These 24 families, when combined with the 150 reported simplex families, totaled 174 simplex families.

Because different proportions of multiplex and simplex families were clinically evaluated and only a subset of reported multiplex families could be confirmed as such, the observed ratio of simplex to multiplex families following clinical evaluation (2.4 to 1) was greater than that obtained from the reported family history (1.5 to 1). To estimate the "true" ratio of simplex to multiplex families if we had been able to examine all of the families to confirm affection status, we performed a Bayesian analysis (15). Using the reported proportions of simplex (174/247) and multiplex (72/247) families, and assuming that all families that were clinically multiplex had been reported to be multiplex while 19 of 49 reported as multiplex families were truly simplex, it was possible to estimate the true proportions of simplex and multiplex families in the original cohort. These calculations predicted that 81.9 percent, or 202 families, would be simplex, and 18.1 percent, or 45 families, would be multiplex. By clinical examination, we were able to confirm 30 families as multiplex, or two thirds of the number expected (the remainder being lost to follow-up or refusing to participate). To maintain the same proportion of simplex to multiplex families, 135 (two thirds of 202) simplex families were selected at random to be included in subsequent analyses. The results described below are thus based on the 30 confirmed first degree multiplex families and 135 simplex families. The latter consists of the 19 multiplex families changed to simplex, the 30 confirmed simplex families, and a randomly selected group of 86 simplex families. There were no differences in proband sex or age at onset between the simplex families included in the analyses (i.e., 165 families) and the 58 simplex families that were not included. The study group consists of only 165 distinct families inasmuch as one family includes two independently ascertained probands.

In any study of a complex disease known to have demographic risk factors, not all families have been exposed to identical risk. Thus, the identification of families with an apparent excess risk of disease may depend not just on the presence of excess numbers of cases but also on other risk factors such as the age and sex of relatives and the pedigree structure. Individuals who are affected by a particular age or who are of a particular sex may signify greater or lesser risk than other affected individuals whose ages of onset or sex conform to population norms. We used a statistical method proposed by Chakraborty et al. (16) for the detection of excess risk of disease in structured data, such as in families, by taking into account known risk factors such as age and sex. Given a known risk distribution for the underlying population from which the sample is obtained, a test statistic is defined that allows one to determine whether a particular family shows excess risk of disease as measured by the numbers of affected individuals when compared with the expected risk for disease given the same number of individuals with the same risk factors drawn at random.
from the population. The test statistic, $T(x)$, is defined as

$$T(x) = \sum_{i=1}^{n} (x_i - p_i)^2 / p_i(1 - p_i),$$

where $x_i = 1$ or 0 depending on whether the ith individual in a family of size $n$ is affected or not. The prior probability that a particular individual is affected, $p_n$, is defined based on age, sex, or other known risk factors from population studies.

For our study, each family member was assigned a prior probability of affection based on age- and sex-specific cumulative incidence estimates for rheumatoid arthritis established by Linos et al. (17). All individuals were considered to be at risk from their date of birth to their date of onset if affected or to their date of death or date of ascertainment (censoring) into this study if unaffected. Probands were necessarily excluded from these analyses, and each family was considered individually. A Bonferroni correction was used to adjust the level of significance for testing each of the 165 families so that the overall significance for familial aggregation was 5 percent; thus, the adjusted level of significance was 0.05/165 = 0.0003.

Student’s $t$ tests were used to compare differences in means for continuous variables, and chi-square tests were used to compare differences in proportions.

**RESULTS**

In our study, a crucial observation was that for a large proportion of families, clinical evaluation did not confirm a diagnosis of rheumatoid arthritis of family members as had been reported initially by the proband in the family history questionnaire. Only 50 of 129 family members reported by the proband as being affected were confirmed as having rheumatoid arthritis, yielding a false-positive rate of 62 percent (i.e., 79 of 129). The results are slightly better when only the first degree relatives who were examined are considered. The false-positive reporting rate for rheumatoid arthritis in first degree relatives was 55 percent. Only 39 (45 percent) of 86 first degree relatives who were reported by the proband as being affected were confirmed to have rheumatoid arthritis after clinical evaluation. One individual who was reported affected met criteria for probable rheumatoid arthritis by 1958 criteria.

In contrast, only one of the 223 family members from either the simplex or multiplex families initially reported as being unaffected clearly had rheumatoid arthritis after clinical evaluation. This individual was truly unaffected at the time the proband completed the family history questionnaire. He subsequently developed rheumatoid arthritis during the 3-year interim period between the initial report of his affection status and the clinical evaluation that sought to confirm his affection status. In addition, two other individuals may have met probable criteria for rheumatoid arthritis; however, both were diagnosed by their private physicians as having gout, but there was no documentation of intraarticular monosodium urate crystals. Although these two individuals did not meet criteria for rheumatoid arthritis, the diagnosis could not be completely ruled out. Given the absence of false-negative cases, in subsequent analyses we assumed that all individuals reported as unaffected were correctly diagnosed, even though they may not have undergone a complete clinical evaluation.

The demographic and clinical characteristics of the 166 probands and their families that were included in subsequent analyses are summarized in table 1. The aggregation analysis revealed that only 18 of the 30 multiplex families had significant excess risk of rheumatoid arthritis inasmuch as the occurrence of multiple cases in the remaining 12 could be explained by chance aggregation. Simplex families by definition have only one affected individual. Therefore, as expected, none of the simplex families demonstrated any excess risk of rheumatoid arthritis. The average age at onset of rheumatoid arthritis was significantly younger in the probands from both types of multiplex families as compared with probands from simplex families: 41.9 and 40.1 years as compared with 47.6 years, respectively ($p < 0.05$). Furthermore, the female to male ratio of probands in the multiplex families was approximately 1 (15:16), which was significantly different from the 2.6 (98:37) ratio seen in the probands from simplex families ($p < 0.02$). There were no significant differences in clinical manifestations of rheumatoid arthritis (i.e., the presence of positive rheumatoid factor, roentgenographic evidence of erosions, rheumatoid nodules, or other extraarticular manifestations such as Felty’s syndrome or vasculitis) among the probands from the three types of families.

Family size, years of accumulated risk in relatives, age of onset of the proband and relatives, as well as the sex of the proband were compared to identify factors that could explain the results of the aggregation analysis. As seen in table 2, the average family size did not vary significantly between the three groups of families (i.e., simplex, multiplex-significant, and multiplex-nonsignificant ($p = 0.8$). Thus, the multiplex-significant families do not show significant excess risk simply because they have more family...
In fact, the average number of years of risk per family is less in the multiplex-significant than in the multiplex-nonsignificant families; however, this difference is not significant \((p = 0.8)\). Although the probands from the multiplex-significant and multiplex-nonsignificant families have similar ages of onset \((p = 0.7)\), the first degree relatives in multiplex-significant families have a significantly younger average age of onset (approximately 10 years) compared with first degree relatives in multiplex-nonsignificant families \((p < 0.006)\), as shown in table 3. The proportion of male and female probands in the multiplex-significant versus the multiplex-nonsignificant families is not significantly different \((p = 0.2)\); however, as stated above, multiplex family probands have an equal sex ratio as compared with simplex family probands. There were no significant differences in clinical manifestations of rheumatoid arthritis between the affected first degree relatives from the two types of multiplex families.

In table 4, the proportion of multiplex to simplex families when the families are classified by proband age of onset is shown. The proportion of multiplex families declines with increasing proband age of onset, from a high of 27 percent \((13/49)\) in families having a proband whose age of onset was less than or equal to 39 years of age to an absence of multiplex families where the proband age of onset was 70 years and older. These results provide additional evidence that an early proband age of onset is a marker for increased familiality. Due to the small number of multiplex families, the chi-square value for linear trend was not significant.

The crude prevalence of rheumatoid arthritis for these first degree relatives is shown in table 5. The prevalence is greater in females as compared with males for parents and siblings; however, these differences are not statistically significant. The very small number of affected children precludes a test for potential sex difference. The prevalence in parents and siblings was similar, whereas the prevalence in children is much smaller than that of either parents or siblings \((p < 0.0001)\). The overall unadjusted rate of rheumatoid arthritis among first degree relatives was 3.2 percent \((40/1,257)\). Of interest, there were no cases of rheumatoid arthritis found among 96 male and 46 female spouses. Using the 1980 data from Linos et al. \((17)\) for the expected general population incidence rates for definite and classic rheumatoid arthritis, we calculated an overall relative risk of rheumatoid arthritis for first degree male relatives to be 12.09 and for first degree female relatives, 10.56.
**DISCUSSION**

This study of the familial risk of rheumatoid arthritis in a consecutive series of patients whose hospital discharge records were ascertained without prior knowledge of their family history provides several important findings with implications for future family studies. A high false-positive rate of reported rheumatoid arthritis among family members was found. In contrast, there were no false-negative cases. A unique aspect of the present study was the determination that less than two thirds of the multiplex families had significant excess risk of rheumatoid arthritis. Furthermore, probands from multiplex families were found to be younger at disease onset and more likely male than probands from simplex families.

The proband report of 32 percent multiplex families of a cohort of 247 families in our study is greater than the report of 16 percent multiplex families from the study of Wolfe et al. (18). Although we had a high false-positive rate (62 percent as compared with 27 percent in the Wolfe et al. study), our estimated proportion rate of multiplex families (18 percent) by clinical evaluation is still higher than their reported rate (10.9 percent). Because our series was based on probands who were identified through a hospital-based registry, it is likely that they had more severe disease than patients identified through an outpatient-based registry. Because the clinical features of patients from the study of Wolfe et al. (18) were not reported, we are unable to compare differences in the clinical features or disease severity between the two studies. Other studies (19, 20) have suggested a lack of association between familiality and disease severity, however.

We found differences in sex and age at onset of rheumatoid arthritis between probands from multiplex families compared with those from simplex families. A younger age at onset among probands from multiplex families was also reported by Del Junco et al. (8) and by Sanders and colleagues (20). In contrast, neither Deighton and Walker (19) nor Wolfe and colleagues (21) found differences in age between familial and sporadic cases of rheumatoid arthritis. Deighton and Walker reported a trend of increased concordance for rheumatoid arthritis in 231 sibships of the same sex (186 females and 45 males) with older proband age, whereas the present study suggests a marked decrease in the proportion of multiplex to simplex families with older proband age at onset (table 2) (19). The reported differences may be due in part to differences in the populations studied. The age at onset of rheumatoid arthritis in probands in that report appears to be older than in the present study. As in other complex disorders with an underlying genetic component, younger age onset is correlated with increased familiality. This implies that, as observed in familial breast cancer wherein genetic cases having a younger age at onset can also occur with sporadic cases having an older age onset in the same family, the appearance of a familial component does not necessarily imply homogeneity in their etiology (22).

We found that probands from multiplex families were more likely to be male, despite the fact that Deighton and Walker (19) reported higher concordance rates among female same-sex sibships than among male same-sex sibships. Although differences based on proband sex were not observed in other studies, of potentially greater importance may be the finding of Weyand et al. (23) that 57 percent of patients who were homozygous for the DRB1 allele 0404 were male versus only 30 percent of those who had one DRB1 0404 allele (23).

Clinical features such as the presence of serum rheumatoid factor, radiographic evidence of erosions, and/or subcutaneous nodules did not significantly differ in probands with an affected first degree relative versus those without. These results were similar to those reported by Del Junco et al., Deighton and Walker, Wolfe and colleagues, and Grennan et al. (8, 19, 21, 24).

The finding that only 18 of 30 (60 percent) multiplex families had excess risk of rheumatoid arthritis...
was unexpected. The occurrence of families that appear to be multiplex but did not show excess risk was not surprising in itself, given that rheumatoid arthritis is a relatively common disease with incidence increasing with age (17). However, the high percentage of these families has important implications for any future family studies that seek to identify specific genetic determinants contributing to the risk of rheumatoid arthritis. The results shown in this study and additional analyses that are being reported separately (15) would suggest that sporadic cases of rheumatoid arthritis are more likely to be female and to have an older age of onset compared with familial forms of this disease. The simultaneous occurrence of sporadic cases in families with genetic cases may yield the appearance of a multiplex family, thus suggesting an underlying homogeneous genetic component in these families when none exists. We used a fairly conservative alpha value for defining multiplex families without significant excess risk, however. Using a less conservative alpha value of 0.0017, there are still seven multiplex families (23 percent) that would be defined as having no significant excess risk of disease. The results (not shown) are essentially the same as those presented in tables 1–3.

We have shown that there is variability in the risk of developing rheumatoid arthritis among first degree relatives. The overall prevalence rates and rates among parents and siblings are similar to those reported by Del Junco et al. (8) from a population-based cohort. The risk for children of the probands is less than that of other first degree relatives and can be explained by the fewer years at risk experienced by these individuals. Some of these individuals might become affected in future years (25), a suspicion that would require long-term follow-up to confirm. As expected, the risk is higher among female relatives than among male relatives. Prevalence rates for second degree relatives were not calculated because further questioning of probands and family members indicated that information about more distant relatives was not reliable and that usually only selected data were reported.
Estimates from twin studies of the genetic contribution to the etiology of rheumatoid arthritis have ranged from 12 to 32 percent (1). The familial clustering of rheumatoid arthritis may be due to a combination of genetic and environmental factors. Several recent reviews have highlighted the roles of potential infectious agents such as parvovirus, Epstein-Barr virus, mycobacteria, and other slow bacterial infections (26-30). Given the limited data available, the role of a specific infectious agent is still speculative, however. Of interest is the lack of any spouses of probands who were found to be affected in the current study.

Because the original cases of rheumatoid arthritis were derived from a referral practice, a potential limitation is an overrepresentation of familial cases due to referral bias. For referral bias to be a major factor influencing the results, males with rheumatoid arthritis who were younger at onset and had relatives with the disease would have to have been referred to (or to have sought care by) this group of practitioners in comparison with women who were older at onset and had relatives with the disease. One possibility is that individuals with severe disease were more likely to have been referred, and familiality may therefore be associated with disease severity. Some studies have reported that males with rheumatoid arthritis have more severe disease than women; however, similar to other studies, we did not find evidence that probands from multiplex families had more severe disease than those from simplex families. In comparing male probands with female probands in our study group, there was no difference in disease severity (i.e., rheumatoid factor positivity, radiographic evidence of erosions, or rheumatoid nodules).

The study focused only on comparison of simplex families with families that had at least one first degree relative affected. The 24 families that had been reported to have second and/or third degree relatives affected were trimmed and included as simplex families. We focused on first degree relatives exclusively for several reasons. There was a greater frequency of false positives among second and/or third degree relatives than among first degree relatives (74 vs. 43 percent). In addition, the information on the numbers and ages of second and/or third degree relatives have been reported in an inconsistent manner. Furthermore,
it was often difficult to contact and confirm the affection status of second and/or third degree relatives inasmuch as the proband often had little contact with these individuals. Probands from reported second degree multiplex families were similar to simplex families in terms of female to male ratio, family size, and clinical features such as percentage of rheumatoid factor positive, percentage with erosions, and percentage with rheumatoid nodules. They differed only in terms of proband age of onset (i.e., the probands from the second degree multiplex families were younger at onset: 40.1 compared with 48.9 years, \( p < 0.02 \)). Therefore the differences in proband age at onset between simplex and multiplex families are likely to be even greater than found in our results, which combined second degree multiplex families with simplex families.

Due to the small number of multiplex families, we have limited power to detect differences between simplex and duplex families. Although the number of multiplex families in this report was similar to those reported in other studies (8, 19), we were also able to show differences in proband sex and age at onset. The results from the present study are similar to those reported by Sanders et al. (20) in that there were no differences in clinical features between affected individuals from simplex and multiplex families even though their group consisted of 52 multiplex families and 214 simplex families.

We have defined the familial risk of rheumatoid arthritis based on a cohort of simplex and multiplex families whose probands were ascertained without regard to their family history of rheumatoid arthritis. Of note, probands from multiplex families differ from probands from simplex families in that probands from multiplex families have a 1:1 male to female ratio and have a younger age of onset. In addition, we found that almost one third of families that appear to have familial cases may actually involve the chance occurrence of two sporadic cases within the same family. These findings have important implications for future studies that seek to identify the role of genetic factors in the etiology of rheumatoid arthritis. These studies should select families with demonstrated excess genetic risk and should focus on probands with younger age at onset and on male probands.

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**REFERENCES**


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