Clinical Usefulness of Genetic Information for Predicting Radiographic Damage in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine whether knowledge of genetic information aids the prediction of radiographic damage for patients with rheumatoid arthritis (RA) in whom extensive sociodemographic, family history, clinical, and immunologic information is available.

Methods. Subjects included 146 Caucasian women who were participants in a community based longitudinal study of RA. Our primary outcome measure was the severity of erosive disease. Nongenetic covariates included age at RA onset, disease duration, family history of RA, education level, family income, baseline values of function, painful and swollen joint groups and pain rating, and rheumatoid factor positivity. All women were genotyped for the HLA-DRB1 shared epitope (SE) and the tumor necrosis factor a (TNFa) microsatellite. Likelihood ratio tests (LRT) were performed to evaluate the usefulness of genetic information for predicting radiographic damage in RA, after adjusting for nongenetic covariates. Receiver operating characteristic (ROC) curves displaying the sensitivity and specificity of combinations of nongenetic and genetic information were derived, and the areas under the curves (AUC) were compared.

Results. Genetic information contributed significantly to the prediction of radiographic damage in RA even after adjusting for all nongenetic covariates (p value for LRT = 0.0019). The odds ratio describing the risk of severe erosive disease among individuals who had inherited both the SE and TNFa allele 11 (TNFa11) was 7.6 compared to individuals who were SE and TNFa11 negative. Analysis of ROC curves confirmed the usefulness of genetic information.

Conclusion. Genetic information is useful for predicting radiographic damage in RA even for patients in whom extensive sociodemographic, family history, clinical, and immunologic information is available. (J Rheumatol 2002;29:2068–73)

Key Indexing Terms:
RHEUMATOID ARTHRITIS PREDICTORS EROSIONS
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Rheumatoid arthritis (RA) is a common inflammatory disease characterized by chronic synovitis and erosive destruction of synovial joints. It is a clinically heterogeneous disorder, with a wide range of outcomes. There is no single prognostic marker for RA[1,2], leading to uncertainty and variation in clinical decision making. This is largely due to practitioners' inability to accurately predict the future course of disease in an individual patient.

Numerous studies support an important role for genetic factors as prognostic markers for RA outcomes[3-5]. In particular, HLA-DRB1 alleles encoding a "shared epitope" (SE) sequence at positions 70–74 of the third hypervariable region have been associated with severe RA. It is likely that other genes also influence RA outcome. For example, we have reported that tumor necrosis factor a microsatellite allele 11 (TNFa11) is associated with RA severity through interaction with the SE[6].

Rapid advances in molecular genetic technology raise the possibility that genetic information may become readily available to practitioners managing patients with RA in the near future. However, clarification of a number of important issues is required before physicians can incorporate genetic information in treatment decisions for RA. For example, several studies indicate that the SE association with RA severity and outcome may be less important for non-

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Caucasian or community based populations[7-9]. Even among Caucasians it is unclear whether genetic information is equally useful later in the disease course, when a wide range of factors (e.g., socioeconomic, treatment, psychological, etc.) have had ample opportunity to influence the course of the disease. Finally, given the wide range of potentially important nongenetic prognostic factors, it is unclear whether genetic information is still useful for predicting RA severity or outcome when a wealth of sociodemographic, clinical, and immunologic information is already available.

We addressed some of these questions utilizing a well characterized sample of 146 Caucasian women with RA. First, we evaluate the contribution of molecular genetic information, specifically the presence of the HLA-DRB1 SE and TNFa11, for predicting radiographic damage after considering the effect of socioeconomic, clinical, and immunologic factors. Next, to illustrate the potential usefulness of genetic information, we describe the variation in probabilities of severe erosive disease among patients with similar nongenetic characteristics but with different genotypes at the DRB1 and TNFa loci. Finally, we derive receiver operating characteristic (ROC) curves to illustrate the sensitivity and specificity of the models for predicting severe erosive disease. The areas under the curves (AUC) for different combinations of nongenetic and genetic prognostic factors are compared to confirm the usefulness of genetic information.

MATERIALS AND METHODS

Study population. The study population included 146 Caucasian females with RA who were under the care of rheumatologists in Northern California and had been followed for up to 14 years as part of a community based longitudinal study of RA. Informed consent was obtained from all patients, and the study was approved by the institutional review board at the University of California, San Francisco. Details of this longitudinal RA panel have been published[10,11]. Study subjects were restricted to Caucasian women to minimize heterogeneity in allelic frequencies across populations, and because RA risk and disease expression are likely to differ between men and women[3,12-14].

Radiographic outcome. Our primary outcome measure was the severity of erosions on radiographs. Radiographs were scored according to the modified Genant method[15]. Individuals in whom the weighted total erosion score was ≥ 29 were classified as having severe erosive disease. This cutoff was chosen because it resulted in 2 categories (severe versus mild erosive disease) of roughly equal size. We also performed sensitivity analyses to determine whether our results were robust to alterations in our definition of severe erosive disease.

HLA-DRB1 typing. All individuals were typed for HLA-DRB1. As a first step, HLA-DRB1 was genotyped by Taq I restriction digestion and Southern blot hybridization[16]. Next, to discriminate allelic variants of HLA-DR4, we used DR4 group-specific polymerase chain reaction (PCR) amplification followed by hybridization with sequence-specific oligonucleotide (SSO) probes using the SSO provided by the Eleventh International Histocompatibility Workshop[17]. We identified subtypes of HLA-DR1 using DR1 group-specific PCR amplification followed by restriction fragment length polymorphism analysis[18]. The following alleles were included in our definition of the SE: 0401, 0404, 0405, 0408, 0409, 0410, 0101, 0102, 1001, and 1402. Each of these alleles except 0410 was present in at least one of our study subjects.

TNFa microsatellite typing. All subjects were also typed for the TNFa microsatellite polymorphism as described by Udalova, *et al*[19]. Thirteen alleles were detected at this locus among these women, and all have been previously described.

Nongenetic covariates. In addition to the genetic factors described above, we considered a number of important nongenetic factors shown to have prognostic significance in RA[1,2]. Several of these variables can be obtained from a patient's history. Specifically, we included age at RA onset, duration of disease at baseline (i.e., at time of entry to the longitudinal study), family history of RA, education level, and family income. The next group of nongenetic variables considered describes current clinical status. We included baseline values of the Health Assessment Questionnaire (HAQ; 0 = no disability to 3 = severe disability), number of painful joint groups (0–13), number of swollen joint groups (0–10), and global pain rating (0–100). Finally, we included the presence versus absence of serum rheumatoid factor (RF), as reported by the patients' rheumatologists. With the exception of RF status and family history of RA, which were treated as dichotomous variables, all other nongenetic covariates were treated as continuous variables.

Statistical analysis. We conducted multivariate logistic regressions examining the relevance of genetic information to the development of severe erosive disease, incorporating available covariate information. A previous analysis of these women revealed strong evidence of interaction between TNFa11 and the SE[6]. Thus for the current study we modeled genotype as the presence versus absence of the SE and the presence versus absence of TNFa11. Our model also allowed for interaction between the SE and TNFa11. The contribution of the genetic information to prediction of severe erosive disease was assessed by likelihood ratio testing. Odds ratios characterizing the association between each of the genetic and nongenetic factors of interest and the development of severe erosive disease were also calculated.

To further illustrate the clinical usefulness of genetic information, we derived the pretest and posttest probabilities of severe erosive disease for patients with similar nongenetic characteristics but different genotypes. These probabilities were calculated based on the fitted logistic models, with and without inclusion of genetic information. For this analysis, we initially defined genotype as the presence versus absence of the SE. We then extended this analysis by also considering the presence versus absence of TNFa11 and its interaction with the SE.

ROC curves were generated for a series of models by varying the cutpoint probability used to separate subjects with and without severe erosive disease, and then plotting the resultant sensitivities against the false positive rates under each model. For a perfectly accurate test, the area under a ROC curve equals 1.0. For a totally random test with no discriminatory power, the AUC will approximate 0.5. We calculated the AUC using the nonparametric method of Hanley and McNeil[20]. Different ROC curves, based on models incorporating different nongenetic and genetic factors but tested on the same group of subjects, were then compared by the nonparametric method of Delong, *et al*[21] utilizing the theory of generalized U-statistics.

ROC curve analyses were programmed in Splus[22]. All other statistical analyses were performed using SAS LOGISTIC and GENMOD procedures[23,24].

RESULTS

Table 1 summarizes the major characteristics of the patients with RA in this study. As shown in Table 1, 72% had at least one copy of the SE and 30% had at least one copy of TNFa11. Radiographs were performed during 1997 and 1998, which was on average 22.4 years (standard deviation 10.8 yrs) after diagnosis of RA.

Table 2 displays the results of our multivariate logistic regression analysis. These results indicate that the genotypic

Table 1. Characteristics of 146 female Caucasian patients with RA.

Characteristic	Mean (SD)
Age at RA onset, yrs	41.4 (13.9)
Disease duration at entry, yrs	9.8 (9.0)
Education, yrs	13.7 (2.4)
Family income, US$	42,500 (17,700)
HAQ score, 0–3	1.08 (0.63)
No. of painful joint groups, 0–13	8.4 (3.2)
No. of swollen joint groups, 0–10	5.3 (2.6)
Global pain rating, 0–100	32.7 (25.0)
	Mean (standard error)
Family history of RA, %	31.7 (4.1)
RF positive, %	80.9 (3.3)
SE positive, %	71.9 (3.7)
TNFa11 positive, %	30.1 (3.8)

SE: shared epitope, TNFa11: tumor necrosis factor a allele 11.

Table 2. Odds ratios derived from multivariate logistic regression depicting the association between nongenetic and genetic characteristics and severe erosive disease. P value for the likelihood ratio test (LRT) of the contribution of genetic information to predicting severe erosive disease is shown.

	OR (95% CI)
Age at RA onset (per 5 years)	0.87 (0.71, 1.07)
Disease duration (per 5 years)	1.4 (1.0, 2.1)
Family history of RA (yes vs no)	1.7 (0.6, 4.8)
Education level (per 4 years)	2.1 (0.9, 4.8)
Family income level (per $10,000)	0.7 (0.5, 0.9)**
Baseline HAQ (per 1.0 units)	5.4 (2.0, 15.1)**
Baseline pain (per 10 units)	1.1 (0.9, 1.4)
Baseline joint pain (per joint group)	1.0 (0.8, 1.2)
Baseline joint swelling (per joint group)	0.9 (0.7, 1.1)
RF positive (yes vs no)	4.8 (1.2, 19.2)**
Genetic information *	7.6 (1.5, 38.4)**
P value for genetic information (LRT)	0.0019

* Odds ratios for the presence of both the SE and TNFa11 versus the absence of both. ** Statistically significant association.

information was statistically significantly associated with severe erosive disease even after adjusting for all available sociodemographic, family history, clinical, and immunologic information (p = 0.0019 for LRT). The OR shown also reveals that this association was clinically significant (OR = 7.6). Sensitivity analyses indicated that our results for severe erosive disease were robust to alterations in our definition of this outcome.

As expected, several nongenetic covariates were also significantly associated with severe erosive disease. Specifically, patients who had lower family income levels and higher baseline HAQ scores and who were RF positive were significantly more likely to develop severe erosive disease (Table 2).

Table 3 compares the estimated probabilities of severe erosive disease for patients with specific characteristics before and after considering the results of genotyping for the SE and TNFa11. For example, considering a typical patient in our study (i.e., with median covariate values), the best predicted probability of having severe erosive disease based on nongenetic information alone is 50.7%. After DRB1 genotyping, the probability of having the same outcome increases to 56.3% if she is SE positive; on the other hand, the probability is reduced to 17.4% if she is SE negative. Information about TNFa11 further influences the probability of severe erosive disease. Considering again the average patient in our study, the probability of severe erosive RA ranges from 3.9% if she is SE negative and TNFa11 positive, to 65.9% if she is both SE and TNFa11 positive. The interaction between the SE and TNFa11 with respect to RA outcomes has been described[6]. Table 3 also displays the influence of genetic information on the probability of severe erosive disease for patients with other sociodemographic, clinical, and immunologic characteristics.

To further illustrate the relative contribution of genetic and nongenetic information for predicting severe erosive disease, we plotted the ROC curves for a series of models that incorporate different combinations of nongenetic and genetic information. ROC curves depict the tradeoff between sensitivity and specificity of a particular "test" or model in this case. Intuitively, the AUC for a particular test corresponds to the probability of correctly ranking a pair of subjects, one with and one without severe disease. Figure 1 displays the ROC curve for predicting severe erosive disease. As expected, the performance of the model improved as we incorporated more information, including genetic information. The AUC (standard error) increased from 0.72 (0.043) for the ROC curve based solely on baseline demographic information to 0.84 (0.034) when baseline clinical information was also included. The AUC increased further when information about RF positivity was included (AUC = 0.85, standard error = 0.033). Finally, when we incorporated information about the presence versus absence of the genetic information (i.e., the SE and TNFa11) into the model the AUC increased to 0.89 (0.027). Given the correlation between the ROC curves, formal comparison of the curves must account for this correlation. When we compared models with and without genetic information, the improvement in AUC of 0.036 was statistically significant (p = 0.015).

DISCUSSION

The results strongly suggest that genetic information contributes significantly to the prediction of radiographic damage in RA even when extensive sociodemographic, family history, clinical, and immunologic information is also available. These findings are particularly noteworthy given that the majority of these women had had their disease for many years before entry into the longitudinal study.

Table 3. Comparison of probabilities of severe erosive disease pre and postgenetic typing, adjusting for nongenetic covariates.

Patient Characteristics	Pretest Probability (%)	Posttest Probability (%)					
		SE		SE/TNFa			
		–	+	–/–	–/+	+/–	+/+
Typical patient*	50.7	17.4	56.3	20.3	3.9	49.7	65.9
Age at onset 60 yrs	37.5	12.6	46.8	14.1	2.5	39.0	55.5
Age at onset 22 yrs	68.4	26.2	68.5	31.6	6.8	64.2	77.8
Disease duration 26 yrs	73.2	44.7	83.2	48.7	13.1	78.7	87.8
Disease duration 2 yrs	44.3	12.9	47.5	15.2	2.8	41.1	57.7
Family history of RA	54.2	20.8	61.6	30.1	6.4	62.5	76.5
Family income $20,000 US	64.8	29.0	71.5	36.6	8.4	69.2	81.4
Global pain rating 75	60.2	27.0	69.4	26.4	5.4	58.3	73.2
Global pain rating 5	45.4	13.3	48.5	17.3	3.2	44.9	61.4
HAQ score 2.06	81.6	45.2	83.5	55.3	16.4	82.8	90.4
HAQ score 0.25	20.8	5.5	26.4	5.5	0.9	18.3	30.5
RF negative	12.5	3.6	18.5	5.0	0.8	17.0	28.5

* A typical patient in our study had an age at RA onset of 44 years, disease duration of 7 years, no family history of RA, a high school education, annual family income of $40,000 US, baseline painful joint count 10, baseline HAQ score 1.125, baseline swollen joint count 6.0, baseline global pain rating 30.0, and was rheumatoid factor (RF) positive. SE: shared epitope, TNFa: tumor necrosis factor a microsatellite.

Therefore, their "baseline" clinical status at enrollment may have already been influenced by their genotypes. The wide range of probabilities of severe erosive disease for patients with similar sociodemographic, clinical, and immunologic characteristics but different genotypes (Table 3) illustrates the potential usefulness of genetic information.

Although the differences in ROC curves for models with and without genetic information do not appear to be strikingly different, it is important to bear in mind that ROC curves depict the tradeoff between sensitivity and specificity of the different models evaluated. They do not reflect the magnitude of association with radiographic damage. The magnitude of the genetic associations is represented by the OR and probabilities shown in Tables 2 and 3, respectively.

Research suggests that RA patients with the DRB1*0401/0404 genotype may experience the worst outcomes[3,25,26]. Only 2 individuals in our study had this genotype, and therefore our results do not reflect a high proportion of such individuals among our SE positive group. We also considered the results of studies that demonstrate an association of TNFa microsatellite allele 6 (TNFa6) with RA susceptibility[27] and severity[28]. None of the other TNFa alleles, including TNFa6, were significantly associated with radiographic damage.

The location of both DRB1 and the TNFa microsatellite in the HLA region raise the possibility that the association of TNFa11 with radiographic damage may be secondary to linkage disequilibrium with HLA-DRB1. However, the data presented in Table 3 indicate that both the SE and TNFa11 influence the risk of radiographic damage. Further, analysis of allelic association between TNFa11 and both the SE and individual DRB1 alleles did not reveal significant linkage disequilibrium. TNFa11 was present among both SE positive and SE negative individuals (data not shown). Similarly, work by others indicates that TNFa11 is present on several ancestral haplotypes with different HLA-DRB1 alleles, both SE positive and SE negative[29].

We chose to focus on radiographic damage in this study because bone erosion is viewed by many as the best measure of the biological activity of the disease. However, because no single outcome measure completely captures the effect of the disease on an individual, we examined several additional RA outcome measures in secondary analyses. Overall, these results were consistent with the results described for severe erosive disease. Specifically, genotypic information was significantly associated with the following outcome measures, even after adjusting for all nongenetic covariates: severe RA course, total joint replacement surgery, and RA hospitalization (data not shown).

Although our data strongly support an important prognostic role for genetic information in predicting severe erosive disease, our study design also imposed several limitations. First, because the patients had well established RA we were unable to evaluate the usefulness of genetic information early in the disease course. Second, because our sample was composed exclusively of Caucasian women, these results may not be representative of all patients with RA, particularly men or non-Caucasians. Previous studies indicate significant genetic heterogeneity corresponding to sex and ethnicity[14,30]. Third, although the DRB1 SE is a well established genetic risk factor for RA, the importance of TNF polymorphism as a predictor of RA outcome remains an area of active investigation[27,31,32]. Fourth, we may have omitted nongenetic (or genetic) characteristics with strong associations with these outcomes. For example, research suggests that psychological characteristics such as self-efficacy and helplessness may have important prognostic significance for some outcomes[33,34]. Finally, we have not

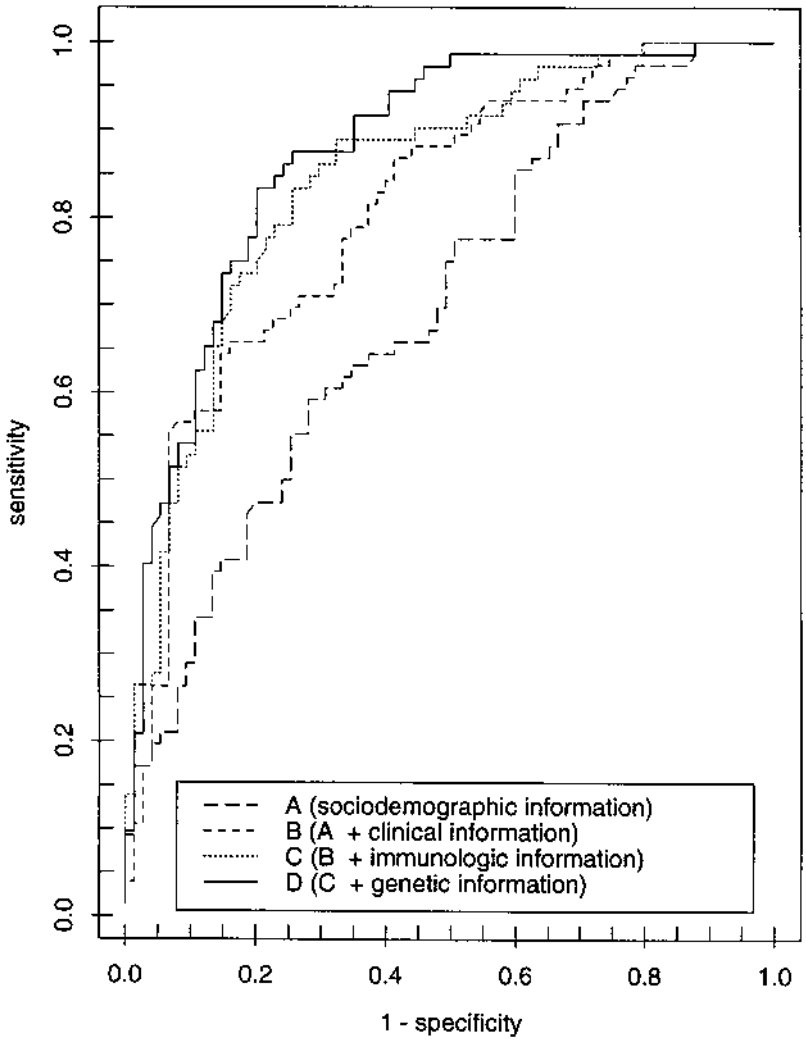

Figure 1. Comparison of ROC curves for predicting severe erosive disease, incorporating nongenetic and genetic information. Curve A corresponds to the logistic regression model that includes age at RA onset, disease duration, education level, income level, and family history of RA. The model for curve B also includes the clinical covariates, specifically baseline values of HAQ score, number of painful and swollen joint groups, and global pain rating. The model for curve C also includes RF status. The model for curve D also includes information about the SE and TNFa11.

considered the relative costs of obtaining the genetic and nongenetic information examined in this study. Currently, genetic information is expensive and generally unavailable. However, this may change markedly in the near future[35,36]. Nonetheless, considering the ease and low expense with which most of the nongenetic characteristics examined can be obtained in routine clinical practice, further work is required to clarify the relative clinical usefulness of genetic and nongenetic prognostic information.

In summary, genetic information contributes significantly to the prediction of radiographic damage in RA, even for patients with well established disease for whom a wealth of sociodemographic, family history, clinical, and immunologic information is available. Further research is required to extend these results to other RA populations and to clarify the relative costs and clinical usefulness of genetic and nongenetic prognostic information.

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