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# Clinical and Immunogenetic Prognostic Factors for Radiographic Severity in Ankylosing Spondylitis

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## Abstract

**Objective—**To improve prognostic ability in ankylosing spondylitis (AS), we sought to identify demographic, clinical, and immunogenetic characteristics associated with radiographic severity in a large cohort of patients.

**Methods—**Patients with AS of 20 years or more were enrolled in a cross-sectional study (N=398). Pelvic and spinal radiographs were scored using the Bath AS Radiology Index-Spine (BASRI-S), and radiographic severity was measured as BASRI-S/duration of AS. Clinical factors and *HLA-B, DR, DQ,* and *DP* alleles associated with the highest quartile of the distribution of radiographic severity were identified by first using random forests and then multivariable logistic regression modeling. Similar procedures were used to identify factors associated with the lowest quartile of radiographic severity.

**Results—**Radiographic severity (being in the top quartile of BASRI-S/duration of AS) was associated with older age of onset of AS (odds ratio (OR) 1.10 per year), male gender (OR 1.90), current smoking (OR 4.72), and the presence of *HLA- B*4100* (OR 11.73), *DRB1*0804* (OR 12.32), *DQA1*0401* (OR 5.24), *DQB1*0603* (OR 3.42), and *DPB1*0202* (OR 23.36), while the presence of *DRB1*0801* was strongly negatively associated (OR 0.03). Being in the lowest quartile of BASRI-S/duration of AS was also less likely among those with an older age of onset of AS (OR 0.94 per year), men (OR 0.28), and current smokers (OR 0.29).

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**Conclusions—**The accuracy of prognosis of radiographic severity in AS is improved by knowing the age of onset, gender, smoking history, and the presence of *HLA-B*4100, DRB1*0804, DQA1*0401, DQB1*0603, DRB1*0801*, and *DPB1*0202* alleles.

### Keywords

ankylosing spondylitis; prognosis; immunogenetics; radiographic severity; random forest

Patients newly diagnosed with ankylosing spondylitis (AS) are often concerned about the future course of their illness, and in particular, about the possibility of spinal fusion. These concerns are well-founded, as the severity of spinal arthritis is an important determinant of health outcomes in patients with AS (1–5). At present, our ability to provide accurate prognostic information for individual patients is poor. Because spinal arthritis is generally progressive and ankylosis is irreversible, radiographic severity increases with the duration of AS (5–9). However, there is substantial heterogeneity in radiographic severity among patients with similar durations of AS, suggesting strong influence of other factors (6,9,10).

Little is known about factors that affect radiographic severity. Men have more severe radiographic changes than women, as do patients with hip arthritis (5,9,10–15). Patients with a history of iritis have been reported to have more severe radiographic changes, particularly in the cervical spine (3,10). Cigarette smoking has been inconsistently associated with radiographic severity (5,16). That few clinical predictors have been identified suggests that radiographic severity may be largely genetically determined. This idea is supported by family studies that demonstrated high heritability of radiographic severity and concordance among siblings (17,18). Although the presence of *HLA-B27* has not been associated with more severe radiographic changes, it is not known if other HLA alleles influence radiographic severity (19–21). Previous studies of immunogenetic associations have not examined radiographic changes, yet radiographic severity is thought to be the feature of AS severity that is most highly genetically influenced (17,18,22–24).

To develop a system that would provide prognostic information in AS, we tested the association of clinical characteristics and immunogenetic markers with radiographic severity in a large group of patients. Because radiographic changes occur slowly, patients with early AS will not have accrued enough time for the severity of radiographic changes to become evident. To reduce misclassification of radiographic severity, we limited the analysis to patients with AS for 20 years or more.

## METHODS

### Patients and Data Collection

Patients were participants in the Prospective Study of Outcomes in AS (PSOAS), and were recruited from clinics of the investigators, local rheumatologists, and from the community (25–27). All patients who met the modified New York criteria for AS (28), were ≥ 18 years old, and were interested in participating in a study of genetics of AS were enrolled. For this analysis, we included patients with AS ≥ 20 years, timed from onset of persistent musculoskeletal symptoms. Patients completed questionnaires on personal and medical history and underwent a clinical evaluation by a study rheumatologist. All patients had phlebotomy for genotyping, and had pelvic and spinal radiographs.

### Clinical variables

Clinical and demographic data included as potential prognostic factors were: age of onset of AS, gender, ethnicity, education level, marital status, smoking history (current, former, or non-smoker, as well as pack-years of smoking), and number of comorbid medical conditions.

Weighted occupational physical activity was calculated based on how much physical activity was performed (little, moderate or much) in each past job and how many years were spent in each job (25). Also included were a family history of AS in a first degree relative, history of inflammatory bowel disease, history of iritis, and self-reported recreational activity in their teens and twenties relative to peers (less = 1, same = 2, or more = 3). Recreational activity was limited to these age groups because previous analyses suggested the level of recreational activity in later years was a consequence of, rather than a predictor of, AS severity.

## Genotyping

Genomic DNA was extracted from peripheral blood leukocytes by standard techniques. *HLA-B* alleles were examined by Sequence Specific Primer (SSP) typing using commercially available kits (Dynal/Invitrogen, Inc.). *HLA-DRB1, DQA1, DQB1* and *DPB1* typing was done by standard oligotyping techniques. High resolution *DRB1* typing was further confirmed by nucleotide sequence analysis of exon 2.

## Radiographic measures

We used the Bath AS Radiology Index-spine (BASRI-S) to assess radiographic severity. The BASRI-S is the sum of scores of the average of the sacroiliac joints, the lumbar spine, and the cervical spine (possible range 0–12) (29). The BASRI-S is a reliable and valid measure of radiographic damage in AS (9,10,30–33). Although other scoring methods may be more sensitive to change, in this study we were concerned with the status of severity, and not with radiographic progression. All radiographs were scored by a single musculoskeletal radiologist (TJL). Intra-reader reliability of the BASRI-S, based on two readings done at least 3 months apart of the films of 50 patients, was 0.987 (95% confidence interval 0.981–0.991).

## Statistical Analysis

We used a two-stage approach to identify prognostic factors: first, using random forests to identify and validate the predictors from among a large group of candidate variables, and second, using logistic regression to determine the strength of association of these predictors with radiographic severity and to build prognostic models.

A random forest is an ensemble classifier that uses multiple classification trees for prediction (34). A single classification tree is a hierarchical procedure that uses recursive partitioning to identify subgroups of patients that are increasingly homogenous with respect to the outcome. For example, the tree program first splits the patient group into 2 subgroups based on the characteristic that best segregates patients in the severe radiographic damage group from those in the lesser damage group. The program then repeats this process for each subgroup until subgroups of sufficient homogeneity are found. The procedure is nonparametric, not model based, and identifies the independent variables that best segregate subgroups of patients.

Random forests work by generating a large number of classification trees. Each tree is developed on a random sample of patients (bootstrap sample with replacement) and uses a randomly sampled subset of independent variables (sampled without replacement) as candidate predictors at each node in the tree. Accuracy of prediction is determined by how well each tree classifies each patient who was omitted from the development of the tree. The proportion of times that a test patient was misclassified by each tree, averaged over all patients, is a relatively unbiased estimate of classification error. This process intensively cross-validates the prediction and obviates the need for separate training and test samples for validation.

The relative importance of independent variables is determined by first counting the number of test patients correctly classified by each tree, then randomly altering the value of one independent variable of the test patients (e.g., changing the sex from male to female randomly),

and determining if the tree correctly classifies these patients. A large difference in the number of patients correctly classified when the independent variable was altered indicates that the variable is important. This difference is averaged over all trees and repeated for each independent variable. We used the mean decrease in accuracy measure to rank the relative importance of predictors. Analyses were performed using the Random Forest in the R library (available at http://cran.us.r-project.org).

Random forests are useful when the number of independent variables exceeds the number of subjects, a situation that limits the application of many conventional statistical methods, but which is common in studies of genetic associations (35). Random forests can also identify rare characteristics as important predictors, whereas these are often excluded from analyses using conventional statistical methods. In addition, random forests are useful for identifying associations with independent variables when none is considered *a priori* to be more important, as was the case with the immunogenetic markers in this study.

Even with limiting the analysis to patients with AS for 20 years or longer, there was a wide range of durations of AS present in the sample. To standardize the measure of radiographic severity further, we defined radiographic damage as BASRI-S divided by the duration of AS, and classified those in the top quartile as having severe damage (BASRI-S/duration $\geq 0.3639$). The duration of AS was dated from the onset of persistent musculoskeletal symptoms, and not date of diagnosis. The candidate predictors included 14 clinical variables and dichotomous variables for each *HLA-B*, *DRB1*, *DPB1*, *DQA1*, and *DQB1* allele (155 variables in total). Alleles were coded as present if one copy was present. Single random forests were constructed of 500 classification trees, using a randomly selected 75% subset of patients, 12 randomly selected independent variables tested at each node, and a weighted voting across trees such that the false-positive rate is then approximately equal to the false-negative rate. This process was repeated for 1000 different random forests.

To refine the prediction, the 30 top-ranked predictor variables from the initial set of random forests were then tested in a second set of 1000 random forests of 500 trees each. While rankings are useful to identify variables of prognostic interest, the rank of any variable is a function of the other variables in the list, and aggregation of rankings from separate lists may not respect the original rankings. Importantly, the relative prognostic importance of two variables is not proportional to their rank order.

Therefore, in the second stage, we developed multivariate logistic regression models to determine the relative strength of association between predictors and radiographic damage. We used the category of radiographic damage as the dependent variable and the top-ranked predictors from the random forests as the independent variables, including at a minimum the top eight ranked variables. These analyses provided adjusted odds ratios that estimated the likelihood that a patient with the clinical characteristic or allele would be in the more severe group. While the random forest is very efficient at detecting important predictors, it is in itself complex. We used logistic regression as an interpretable reference model. These analyses were performed using SAS programs (SAS Institute, Cary, NC).

The random forests were developed using 385 patients (of 402 patients in the cohort) who had complete data (excluding 4 patients with missing data on pack-years of smoking and 13 patients who lacked genotype information for any locus (missing, untypable, or new allele)). The logistic regression models were developed using 398 patients, excluding 4 patients with missing data on pack-years of smoking.

Because predictors of mild radiographic damage may be different from predictors of severe damage, we repeated the random forest analysis using patients in the lowest quartile of BASRI-S/duration of AS as the group of interest (BASRI-S/duration $< 0.1780$). We also repeated the

analysis comparing patients in the top tertile to those in the bottom tertile, but this analysis did not provide additional insights.

# RESULTS

## Patient characteristics

The features of the patients (N=398) are shown in Table 1. The mean duration of AS was 31.8 years. The cohort was comprised mostly of men, and 87% were *HLA-B27* positive. Immunogenetic markers were highly polymorphic, with 45 different *HLA-B* alleles, 38 different *DRB1* alleles, 16 different *DQA1* alleles, 15 different *DQB1* alleles, and 21 different *DPB1* alleles among our patients. Three *HLA-B* alleles were present in > 10% of patients (*B*2705*, *B*4400*, and *B*0800*). Similarly, one *DRB1* allele *(*0101*), five *DQA1* alleles *(*03, *0101, *0102, *0201*, and *0501*), five *DQB1* alleles *(*0301, *0302, *0501, *0602 and *0201*), and four *DPB1* alleles *(*0401, *0402, *0301, and *0201*) were present in > 10% of patients.

The median BASRI-S score was 9. The mean (± standard deviation) BASRI-S/duration was 0.283 ± 0.13. The median (interquartile range) BASRI-S score was 11.5 (10–12) among those in the highest quartile of BASRI-S/duration, and 3.5 (3–6) among those in the lowest quartile.

## Associations with severe radiographic damage

We evaluated the association of 14 clinical variables and all *HLA-B, DRB1, DQA1, DQB1,* and *DPB1* alleles with radiographic severity, using the 75$^{th}$ percentile of BASRI-S/duration as the threshold for severe damage. Among the 1000 random forests, age of onset of AS was consistently ranked as the most important variable (Figure 1). The alleles *DRB1*0801, DRB1*0804, DQA1*0401*, and *HLA-B*4100* were the next most highly ranked, followed by *DQB1*0603*, current smoking, and male gender, and *DPB1*0202*, although these were less consistently associated with severe radiographic damage among different random forests. The overall misclassification error was 30.34% ± 2.29%.

We next developed a multivariate logistic regression model to determine the strength of association between severe radiographic damage and variables identified as important in the random forests (Table 2). The likelihood of being in the group with severe damage increased with age of onset of AS, and men were almost twice as likely as women to be in this group. Current smokers were more than four times as likely as former smokers or nonsmokers to be in the severe group. Among the immunogenetic variables, *HLA-B*4100, DRB1*0804, DQA1*0401, DQB1*0603,* and *DPB1*0202*, were strongly associated with more severe radiographic damage. In contrast, adjusting for the other variables in the model, patients with *DRB1*0801* were much less likely to be in the group with severe radiographic damage (adjusted odds ratio = 0.03). The model fit the data well (c statistic = 0.80; Hosmer-Lemeshow test p = 0.38). Variables ranked tenth and eleventh in the random forests were not significantly associated with severe radiographic damage, and were not included in the final model.

Significant associations were present even though some immunogenetic alleles were uncommon. *HLA-B*4100* was present in 6 patients (1.5%), *DQA1*0401* in 38 patients (9.5%), *DQB1*0603* in 33 patients (8.3%), *DRB1*0804* in 6 patients (1.5%), *DRB1*0801* in 24 patients (6.0%), and *DPB1*0202* in 4 patients (1.0%). *DQA1*0401* and both *DRB1*0801* and *DRB1*0804* are known to be in linkage disequilibrium, but in this analysis *DQA1*0401* was associated with more severe radiographic damage, while *DRB1*0801* was protective. Of the 38 patients who had *DQA1*0401*, 21 also had *DRB1*0801* and 17 did not. None of the 21 patients with *DRB1*0801* were in the severe radiographic group, while 12 of the 17 (70%) of those who were *DQA1*0401*-positive but *DRB1*0801*-negative were in the severe group,

accounting for the divergent associations found for these linked alleles and indicating that the protective effect of *DRB1*0801* dominated the effect of *DQA1*0401*.

The probability that a patient would be in the severe radiographic group was computed from the logistic model for men and women at three different ages of onset (23.1 (the group mean), 18 or 30 years), among current smokers and nonsmokers, and for selected combinations of HLA alleles (Table 3 and Appendix). For the base case of a nonsmoking man with onset of AS at age 23.1 years, the probability of being in the severe radiographic group was 0.188 in the absence of any of the risk alleles. This probability increased to over 0.70 if either *HLA-B*4100* or *DRB1*0804* was present. This probability was 0.932 if both *DRB1*0804* and *DQA1*0401* were present, but decreased dramatically if *DRB1*0801* was present. The probability of being in the severe radiographic group was lower among women than men for any combination of prognostic factors.

### Associations with less severe radiographic damage

Because the identification of prognostic factors for mild AS may also be useful, we used the same approach to examine variables associated with less severe radiographic changes, using the $25^{th}$ percentile of BASRI-S/duration as the threshold for distinguishing milder from more severe radiographic damage. In this analysis, gender was consistently ranked highest (Figure 2). Age of onset of AS was the next most highly ranked variable, followed by two variables characterizing smoking status, *DRB1*0901* and *DQA1*0102*, ethnicity, and recreational activity in teens and twenties. The overall misclassification error among random forests was 36.334% ± 2.74%.

We used the variables ranked highest as input for the multivariate logistic model to assess the strength of their associations with less severe radiographic damage (Table 4). The likelihood of being in the less severe group was lower for those with an older age of onset, men, and current smokers. Patients with *DQA1*0102*, who comprised 30% of the sample, were somewhat less likely to be in the less severe group, while those with *DRB1*0901* were somewhat more likely to be in this group. The model fit the data well (c statistic = 0.75; Hosmer-Lemeshow test p = 0.65). No other highly-ranked variables were significantly associated with membership in the less severe group. In a separate model that included pack-years of smoking instead of smoking status, those with a history of more than 20 pack-years (adjusted odd ratio = 0.53; 95% confidence interval 0.25, 1.10; p = .09) were somewhat less likely to be in the less severe group, compared to non-smokers.

## DISCUSSION

Accurate prognostic information can be used to counsel patients about their illness and its future course. It also allows risk stratification, which can be used in clinical trials to select the subgroups of patients most at risk for the outcome of interest, thereby improving the efficiency of the trial. Radiographic severity is an important outcome for which to identify prognostic markers, because the degree of spinal damage is highly variable among patients, it affects health outcomes of concern to patients, and because testing of treatments for their ability to slow radiographic damage is of great interest.

Our prognostic model differentiated patients at risk for severe radiographic damage based on a small set of clinical variables and HLA markers. The key prognostic variables were identified and validated using random forests, a statistical learning machine scheme that allows testing for the associations of a large number of candidate predictors. With this approach, we were able to identify several alleles of prognostic importance among the highly polymorphic HLA markers. Nineteen percent of patients had at least one of the five HLA alleles prognostic for severe radiographic damage, and 7.8% had two or more of these alleles. Among these patients,

the presence of these risk alleles greatly changed the probability that severe radiographic damage was present, demonstrating that even if alleles are uncommon, they can be jointly predictive with good accuracy. In the remaining patients, prognostic information was contributed by age of onset, sex, and smoking status. These 3 variables can be used to estimate the likelihood of severe radiographic damage after 20 years of AS, with the probability being higher for men, smokers, and those with onset at an older age.

Men with AS had more severe radiographic damage than women, confirming previous studies (5,9,10–15). We also found that the likelihood of more severe damage was greater among those with an older age of symptom onset. This association may result if these patients have more extensive spinal inflammation or are more prone to bone formation. Some (27,36,37), but not all (5,10), studies support this possibility. This association may also result if patients with an older age of onset are more likely to be asymptomatic early in their illness, or to have stuttering or milder symptoms, which might cause them to underestimate the duration of their AS. *HLA-B27* alleles were not associated with radiographic severity, supporting previous studies (19–21).

Of the HLA alleles found to be associated with radiographic severity, *HLA-B*4100*, *DRB1*0804*, *DQA1*0401*, *DQB1*0603*, and *DPB1*0202* were associated with an increased risk of radiographic severity. Although the presence of *DRB1*0801* was associated with a decreased likelihood of being in the highest 25% of the distribution of BASRI-S/duration of AS, this does not necessarily mean that patients with this allele had mild radiographic changes; they could have had "average" radiographic severity. We do not know if these alleles are related mechanistically to the development of radiographic damage in AS, or if they are linked to other genes that are directly related. *HLA-DRB1*0801* differs from *DRB1*0804* at two amino acid positions crucial in antigen binding and T cell receptor interaction, although how this might influence radiographic severity is unknown. However, the absence of information about the pathogenetic importance of these alleles does not diminish their prognostic value, in the same way that absence of information about the ways in which male gender influences radiographic severity does not diminish its prognostic value.

Men, patients with an older age of onset, and current smokers were not only more likely to be in the group with more severe radiographic damage, but were also less likely to be in the group with relatively little radiographic damage. This finding emphasizes the importance of these factors in stratifying risk. Two previous studies of the association between smoking and radiographic severity in AS reported conflicting results (5,16). However, smoking has been consistently associated with more severe limitations in physical function in patients with AS, suggesting indirectly that smoking may increase skeletal damage (5,16,25,38,39). Although patients who had *DRB1*0901* were over three times more likely than those without this allele to be in the less severe group, this association was marginally statistically significant. Those with *DQA1*0102* were somewhat less likely to be in the lowest quartile of radiographic severity, indicating an increased risk for "average" or severe radiographic damage among these patients.

The strengths of this study include the large well-characterized sample, examination of a number of clinical characteristics and HLA loci, and testing of prognostic factors for both severe and less severe radiographic damage. The use of random forests allowed us to test and validate associations of the highly polymorphic HLA alleles, even in this circumstance when the ratio of the number of alleles to the number of subjects was relatively high. However, the misclassification error rates suggest that prediction of the random forests could be improved, and indicate that additional prognostic factors are still to be discovered. These additional factors are likely to be other genetic markers, which can be easily incorporated in extensions of this model. The relative importance of HLA alleles will best be determined after other prognostic

markers have been identified and the strengths of their association estimated. Other prognostic markers may be more common but have weaker associations with radiographic severity. This study is limited in that we did not examine AS activity or certain clinical features, such as nonsteroidal anti-inflammatory use, as potential prognostic factors due to the absence of complete historical data. Prognostic variables were either time-invariant or able to be assessed at the time of diagnosis of AS. We likely underestimated radiographic severity in some patients who had reached the maximum BASRI-S score. We limited the study to patients with AS ≥ 20 years to allow time for patients to develop radiographic changes and minimize false negative associations of the prognostic variables. Timing the onset of AS can be imprecise. Inaccurate recall may have introduced variation, but recall would not be expected to vary by HLA status, and therefore would not confound associations with HLA alleles. BASRI scores in this cohort were similar to those of patients with 20 or more years of AS in other reports, suggesting the sample was not atypical with respect to radiographic severity (9).

Our models demonstrate that age of onset, gender, smoking history, and selected HLA alleles predict radiographic severity in AS. The models can easily incorporate new genetic markers as they are discovered, to provide updated prognostic estimates that are able to stratify risks. In addition to their prognostic importance, the HLA associations can be investigated for potential clues to the pathogenesis of radiographic damage in AS.

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## Appendix

## APPENDIX

Probabilities in Table 3 were calculated from the logistic regression model using the formula

$$\Pr=(1+e^{-Z})^{-1}$$

where for estimating the probability of being in the severe damage group, z = −4.5442 + .1035 (age of onset) + .644(male) + 1.552(current smoker) + 2.4625(*HLA-B*4100*) + 2.5115 (*DRB1*0804*) − 3.6233(*DRB1*0801*) + 1.6574(*DQA1*0401*) + 1.2295(*DQB1*0603*) + 3.1513 (*DPB1*0202*).

For estimating the probability of being in the less severe damage group, z = .696 − .0686(age of onset) − 1.2788(male) − 1.2613(current smoker) + .491(white) + .182(recreational exercise level) + 1.3464(*DRB1*0901*) − .5692(*DQA1*0102*).

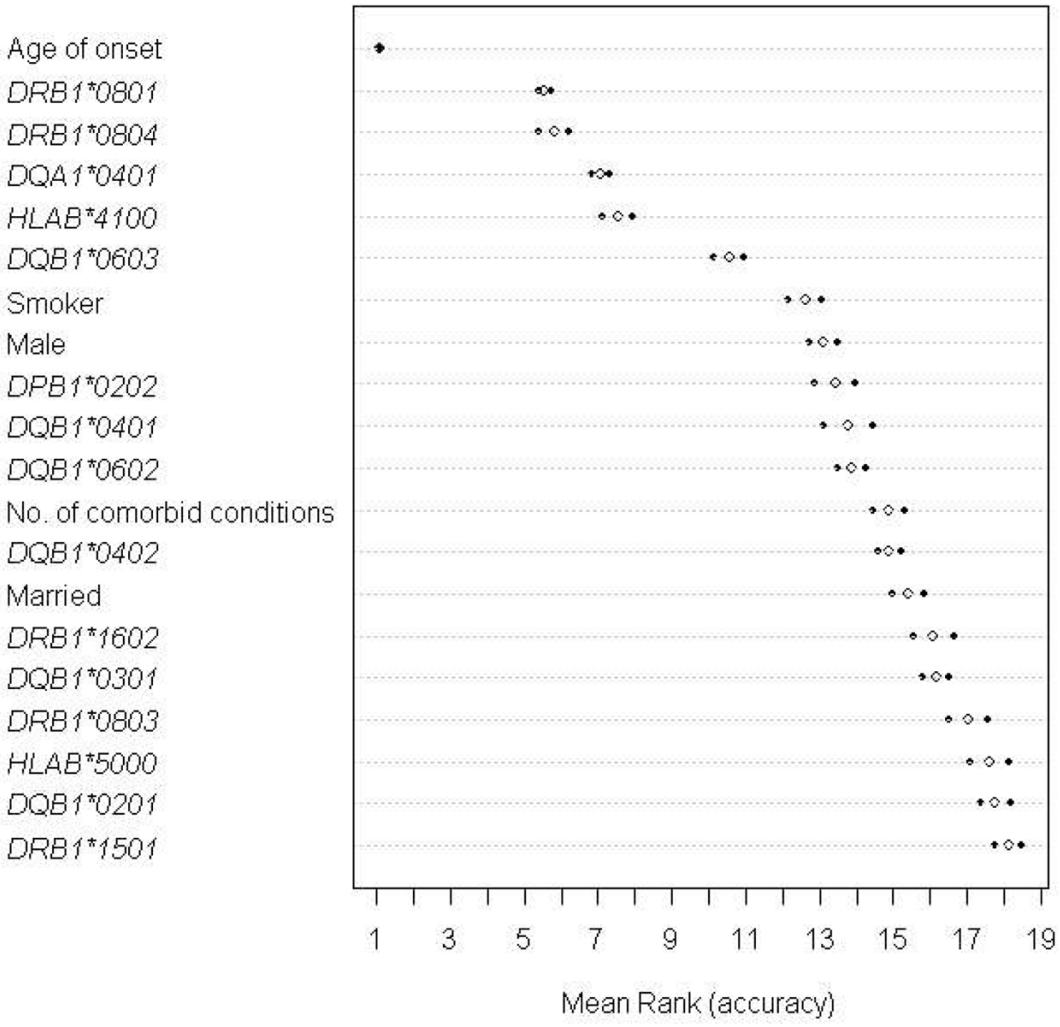


**Figure 1.**
Rank order of prognostic factors for identifying patients with severe radiographic damage (in the highest quartile of the distribution of BASRI-S/duration), based on 1000 random forest runs, each with 500 trees. Values are the mean rank ± standard error.

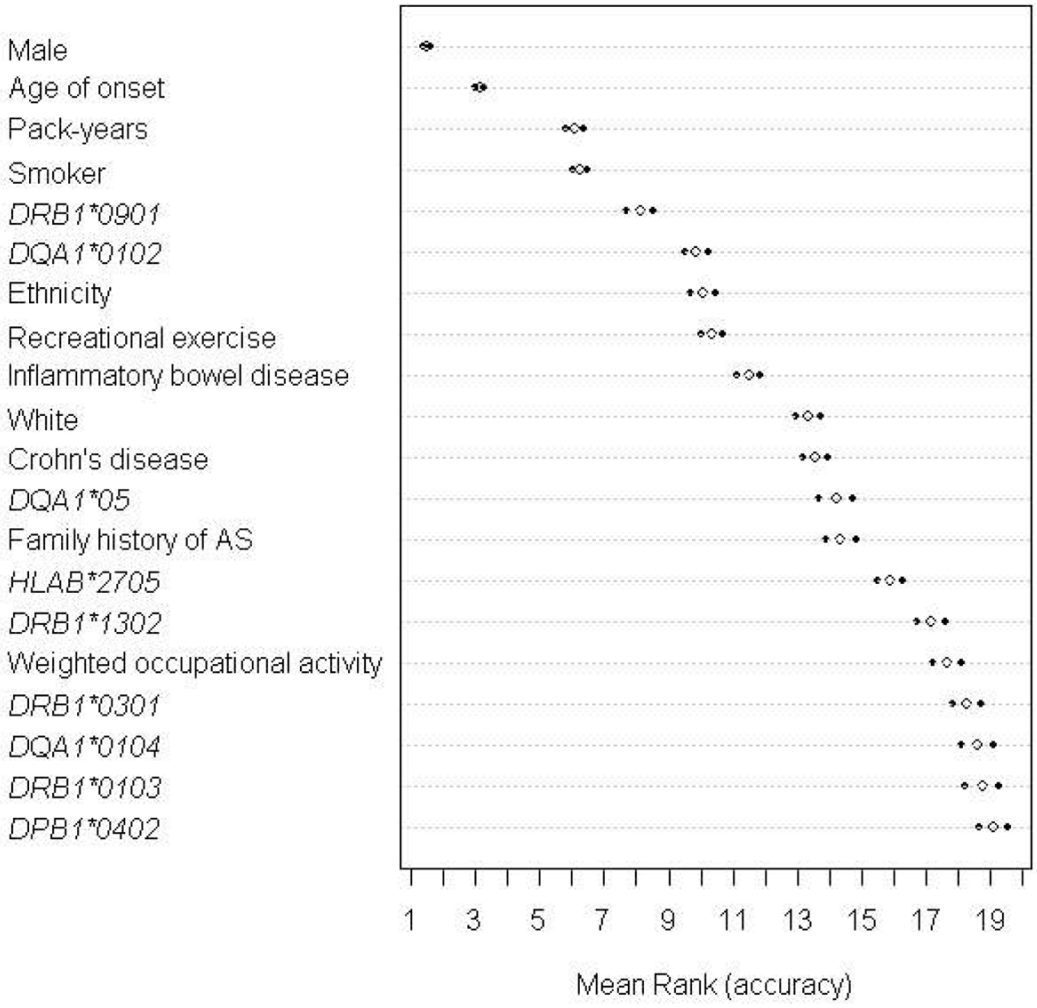


**Figure 2.**
Rank order of prognostic factors for identifying patients with less severe radiographic damage (in the lowest quartile of the distribution of BASRI-S/duration), based on 1000 random forest runs, each with 500 trees. Values are mean rank ± standard error.

**Table 1**

Patient characteristics at study entry (N = 398).

| | |
|---|---|
| Age, years | 55.0 ± 10.8 |
| Age of onset of AS, years | 23.1 ± 7.8 |
| Duration of AS, years | 31.8 ± 10.0 |
| % Male | 75 |
| % White | 88 |
| % Black | 4 |
| % Asian/Pacific Islander | 2 |
| % Native American | 1 |
| % Hispanic | 4.5 |
| % Other | 0.5 |
| Education level, years | 16.0 ± 3.0 |
| % Married | 66 |
| Weighted job activity (0–3) | 1.8 ± 0.7 |
| Recreational exercise in teens and twenties (0–3) | 2.1 ± 0.6 |
| % Non-smoker | 45 |
| % Former smoker | 45 |
| % Current smoker | 10 |
| Pack years of smoking, all patients | 11.3 ± 18.7 |
| Pack years of smoking, ever smokers only | 20.4 ± 21.1 |
| Number of comorbid conditions, % | |
| 0 | 9 |
| 1 | 22 |
| 2 | 26 |
| 3 | 17 |
| 4 or more | 26 |
| % Family history of AS | 28 |
| % History of inflammatory bowel disease | 4.5 |
| % History of iritis | 42 |
| % *HLA*B27* positive | 87 |
| Bath AS Functional Index (0–100) | 40.9 ± 26.5 |
| Bath AS Radiology Index-Spine (0–12) | 8.5 ± 3.2 |

Plus-minus values are mean ± standard deviation. All other values are percents. Values in parentheses are the possible ranges for the measure. AS = ankylosing spondylitis.

**Table 2**

Prognostic factors for severe radiographic damage (being in the highest quartile of the distribution of BASRI-S/duration of AS), by multivariate logistic regression analysis. All variables were included in the model.

| | Adjusted Odds Ratio | 95% Confidence Interval | P |
|---|---|---|---|
| Age of onset, per year | 1.10 | 1.07, 1.15 | <.0001 |
| Male | 1.90 | 0.97, 3.74 | .07 |
| Current smoker | 4.72 | 2.16, 10.30 | <.0001 |
| *HLA B*4100* | 11.73 | 1.07, 127.82 | .05 |
| *DRB1*0804* | 12.32 | 1.05, 143.63 | .05 |
| *DRB1*0801* | 0.03 | 0.002, 0.31 | .004 |
| *DQA1*0401* | 5.24 | 1.35, 20.33 | .02 |
| *DQB1*0603* | 3.42 | 1.43, 8.16 | .006 |
| *DPB1*0202* | 23.36 | 1.87, 291.87 | .02 |

**Table 3**

Probability of being in the highest quartile of the distribution of BASRI-S/duration of AS, based on the presence of different prognostic factors. Probabilities were computed separately for men and women.

| Age of onset | Current smoker | *HLA-B*4100* | *DRB1*0804* | *DRB1*0801* | *DQA1*0401* | *DQB1*0603* | *DPB1*0202* | Probability Men | Probability Women |
|---|---|---|---|---|---|---|---|---|---|
| 23.1 | – | – | – | – | – | – | – | .181 | .104 |
| 18.0 | – | – | – | – | – | – | – | .115 | .064 |
| 30.0 | – | – | – | – | – | – | – | .311 | .192 |
| 23.1 | + | – | – | – | – | – | – | .511 | .354 |
| 23.1 | – | + | – | – | – | – | – | .721 | .577 |
| 23.1 | – | – | + | – | – | – | – | .731 | .588 |
| 23.1 | – | – | – | – | + | – | – | .537 | .378 |
| 23.1 | – | – | – | – | – | + | – | .43 | .284 |
| 23.1 | – | – | – | – | – | – | + | .838 | .731 |
| 23.1 | – | – | – | + | – | – | – | .006 | .003 |
| 23.1 | + | + | – | – | – | – | – | .924 | .865 |
| 23.1 | – | – | + | – | + | – | – | .935 | .882 |
| 23.1 | – | – | – | + | + | – | – | .030 | .016 |

**Table 4**

Prognostic factors for less severe radiographic damage (being in the lowest quartile of the distribution of BASRI-S/duration of AS), by multivariate logistic regression analysis. All variables were included in the model.

| | Adjusted Odds Ratio | 95% Confidence Interval | P |
|---|---|---|---|
| Age of onset, per year | 0.94 | 0.89, 0.97 | .0005 |
| Male | 0.28 | 0.16, 0.48 | <.0001 |
| Current smoker | 0.29 | 0.09, 0.85 | .03 |
| White | 1.63 | 0.71, 3.74 | .25 |
| Recreational exercise during teens/twenties, per 1 unit | 1.20 | 0.79, 1.81 | .39 |
| *DRB1*0901* | 3.84 | 0.94, 15.61 | .06 |
| *DQA1*0102* | 0.57 | 0.31, 1.02 | .06 |