CLINICAL AND GENETIC VARIABLES ASSOCIATED WITH DISEASE SEVERITY AND RISK CORRELATE WITH RADIOGRAPHIC CHANGES IN A COHORT OF SUBJECTS WITH RHEUMATOID ARTHRITIS

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Background

- Several studies identified acute phase response markers, HLA DR gene polymorphisms and RF as predictors of erosive disease in RA
- But most are derived from single cohorts and need independent confirmation (except the HLA DR data)

Objectives

- To identify clinical and genetic markers for erosive disease to identify patients needing aggressive therapy

Registry	Structure	Data/specimens collected
B.R.A.S.S.	1000 RA patients per year for five years (30% new onset RA)	Physician data (yearly) Patient reported data (q6mon) DNA (once); RNA (yearly) Serum (yearly) Whole blood (fresh; yearly)

Methods

Patients enrolled in **BRASS** registry collecting:

- Demographic data
- Description of joint swelling, tenderness, erosions
  - Radiographic changes defined as erosions with or without peri-articular osteopenia reported by physicians who reviewed prior radiographs on all subjects
  - Joint exams by physicians
- DNA, RNA and proteomic data
  - Genetic markers known to be associated with both RA risk and severity were genotyped by PCR and then individually
  - HLA DRB1 Shared Epitope, MMP3 Polymorphism

BRASS Registry, first patient recruited March 2003:

- 711 recruited to date, with 9 dropouts and 61 refusals
- Preliminary six month follow-up rate of 90% after mailing

Statistical Methods

- Logistic regression analysis predicting history of radiographic changes removing independent variables with SE that included zero
- Regression on 244 with complete data

Results

BRASS Cohort Variables
Mn(SD) or %
(n=703)

- Age 57.3 yrs (13.7)
- Sex 82% female
- Duration of disease 14.4 yrs (12.2)
- CRP 10.3 (16) (n=435)
- Rheumatoid nodules 39%
- RF (>15 mg/dl) 64%
- Hydroxychloroquine 16%
- Anti-TNF 37%
- Swollen joint count 8.1 (7.3)
- HLA SE 43%
- MMP3 9.6%

Variables Associated with Radiographic Change
(n=244)*

Variable	Coefficient	S.E.	P value
Age	0.038	0.014	<0.0001
Diag. Dur	0.051	0.020	<0.0001
Nodules	0.861	0.253	<0.0001
RF +	0.448	0.196	0.006
Anti-TNF	0.640	0.225	0.001
MMP3 snp	-0.819	0.401	0.036

*Full model OR=12.7 (95% CI 5.7-28.7)

Results

Variables Associated with Radiographic Change
(<10 yrs RA, n=85)*

Variable	Coefficient	S.E.	P value
Age	0.034	0.018	0.06
HLA SE	1.035	0.405	0.010
Nodules	0.508	0.374	0.003
RF +	0.948	0.561	0.019
Sjogren's	-0.573	0.424	0.223
MMP3.snp	-0.821	0.61	0.15
SJC	0.111	0.052	0.018

*Full model OR=12.1 (95% CI 3.9-38.8)

Conclusions

- The HLA DRB1 Shared Epitope and clinical factors such as age and RF identify patients at risk for poor radiographic outcomes
- A polymorphism within the MMP3 gene may identify patients who have a low risk of erosive disease