GENETIC POLYMORPHISMS CONTRIBUTE TO CLINICAL MARKERS AS PREDICTORS OF DAS REMISSION IN PATIENTS WITH RHEUMATOID ARTHRITIS

Nancy A. Shadick[1], Michael E. Weinblatt[1], Nancy E Maher[1], Joanne Meyer[2], Julie Lekstrom-Himes[2], Geoffrey Ginsburg[2], Heather Matthews[1], Jessica A Bilics[1], Julie E. Karlson[1], Ronald Anderson[1], Daniel H. Solomon[1], Jonathan Coblyn[1], Alex Parker[2]

Division of Rheumatology, Immunology & Allergy, Brigham & Women's Hospital, Boston, MA[1]

Millennium Pharmaceuticals, Cambridge, MA[2]

Background

- Early and aggressive therapy in RA is important in reducing long-term disability and poor outcomes.
- But genetic and clinical predictors remain little understood.

Objectives

- To identify clinical and genetic markers associated with disease remission defined by DAS-CRP score (<2.6)

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, clinical, radiographic and functional status data including joint count
- 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, NFKB1L1 (modulator of the NFkB pathway), TNFRSF11B-osteoprotegerin (negative regulator of bone resorption), SLC11A1 (NRAMP1) ion channel involved in neutrophil function

Statistical and clinical methods:

- DAS defined by: tender and swollen joint count, CRP, VAS
- Logistic and linear regression analysis predicting DAS score and DAS remission using stepwise analyses included independent variables associated with disease severity

Results—BRASS Cohort Descriptors

- 711 recruited, with 9 dropouts and 61 refusals; first patient March 2003
- Preliminary six month follow-up rate of 90% after mailing

Results—DAS Score

n=703

- Age 57.3 yrs (13.7)
- Sex 82% female
- Duration of disease 14.4 yrs (12.2)
- RF (>15 mg/dl) 64%
- Swollen joint count 8.1 (7.3)
- Erosions 74%
- Rheumatoid nodules 39%
- Sjogren's 15%
- Mean DAS 4.1(1.6) n=435
- Fatigue 40.8 (29.2)
- Flares 72%
- Hydroxychloroquine 16%
- Anti-TNF therapy 37%
- Steroid use 33.3%
- MTX 46%
- HLADRB1
- CRP 10.3 (1.6) n=435
- # in DAS Remission 18.6%

Variables Associated with DAS Score*

(n=256)

Variable	*Coefficient*	*S.E.*	*P value*
Rad change**	0.32	0.098	0.00020
Steroid use	0.0090	0.0030	0.020
Age	0.24	0.13	0.0013
Nodules	0.011	0.0070	<0.0001
Fatigue	0.434	0.114	0.0031
NFKB1L1	2.50	0.457	0.020
SLC11A1	-0.24	0.14	0.018
TNFRSF11	-0.25	0.131	0.010

*Full model r2=26% (p<0.00001)

**Radiographic changes defined as erosions with or without peri-articular osteopenia reported by physicians who reviewed prior radiographs on all subjects

Results—Active Disease v. Remission

Variables Associated With DAS Active Disease (5.1) v. Remission (2.6)* (n=136)

Variable	*Coefficient*	*S.E.*	*P value*
Nodules	-0.509	0.250	0.0001
Age	-.034	0.018	0.001
Radiographic change	-0.887	0.289	0.002
NFKB1L1	0.79	0.354	0.022
SLC11A1	0.72	0.348	0.030
TNFRSF11	-1.025	0.34	0.0013

*Full model OR=13.3 (p<0.0001)

Conclusions

- Certain genetic and clinical markers can distinguish individuals who have achieved remission in longstanding RA.
- The genetic markers are polymorphisms involved in the NFkB regulatory cascade, osteoclast maturation and neutrophil function. The clinical markers are those, such as the presence of nodules, fatigue and radiographic changes, that characterize severe disease.