The Associations Between RA Genetic Risk Alleles and Seropositive but Non-erosive Rheumatoid Arthritis

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Introduction

Presently, little is known about the subgroup seropositive rheumatoid arthritis (RA) patients who never develop bone erosions in contrast to those with erosions that remain stable or progress despite treatment.

Objective

Determine whether RA specific risk alleles are associated with remaining erosion-free in a seropositive RA cohort

Methods

Study population

- Selected from the Brigham Rheumatoid Arthritis Sequential Study **(BRASS),** a prospective observational cohort of RA patients recruited from the Brigham and Women's Arthritis Center between 2003-2004
- *Inclusion criteria:*
  - Age> 18 years
  - Diagnosis of RA by rheumatologist
  - RF or anti-CCP positive
  - Bilateral hand radiographs at baseline and 2 year follow-up
  - Sharp score assessed for baseline and follow-up radiograph

Primary outcome

- Erosion score ≤ 3 at baseline and 2 year follow-up

Laboratory methods

Blood samples were genotyped for 31 RA risk alleles and for the HLA-SE alleles on the Affymetrix GeneChip 6.0 at the Broad Institute (Cambridge, USA). Quality control steps included filtering SNPs and individuals with ≥5% missing data, minor allele frequency ≥0.01 and testing for Hardy-Weinberg Equilibrium.

Statistical analysis

- Univariate analysis to compare baseline characteristics of subjects with erosions and those who were erosion-free at baseline and year 2
- Association between risk allele and erosion-free status were assessed using logistic regression models adjusting for age gender and disease duration (age, gender and disease duration were the only significant clinical predictors for erosion-free status from a previous study conducted in BRASS)
- The contribution of genetic information was quantified using OR and 95% CI calculated from the logistic regression models
- Significance after Bonferroni correction was p<0.002

Sensitivity analysis

- Limit disease duration to ≤10 years and test significant SNPs from primary analysis using logistic regression adjusting for age, gender, and disease duration

Results

- 311 RA subjects with genotype information and Sharp scores
- 51 (16.4%) were erosion-free at baseline and 2 years (**Table 1**)

Table 1. Characteristics of seropositive RA subjects who remained erosion-free compared to subjects with erosions in BRASS, n=311

Baseline characteristics	Erosion-free, n=51	Erosions, n= 260	P-value
Mean age at onset (SD)	44.0 (10.8)	41.9 (14.1)	0.31
Female (%)	41 (80.4)	215 (82.7)	0.69
Disease duration, yrs (SD)	7.8 (8.7)	18.3 (12.2)	<0.0001
Ever smoker (%)	26 (53.1)	131 (53.0)	0.99
DAS28 (SD)	3.9 (1.7)	4.3 (1.6)	0.27
Serology			
RF+, n (%)	38 (74.5)	206 (79.2)	0.45
Anti-CCP+, n (%)	48 (94.1)	251 (96.5)	0.41
Medications			
Methotrexate (%)	11 (44)	143 (50)	0.68
Anti-TNF (%)	11 (44)	129 (45.1)	0.92

3 SNPs were independent predictors of erosion-free status after adjusting for clinical factors (**Table 2**):

1. ***TRAF6*** (rs540386, risk allele=common allele C), p=0.04
   encodes mediator involved in induction of T cell tolerance
2. ***L2-IL21*** (rs6822844, risk allele=common allele G), p=0.04
   function unclear
3. ***REL*** (rs13031237, risk allele=rare allele T), p=0.04
   encodes a component of the osteoclastogenesis pathway

For all 3 SNPs, subjects carrying the RA risk alleles were less likely to remain erosion-free.

Table 2. Multivariate models for association between clinical variables and SNPs, (a) *TRAF6*, (b) *IL2-IL21*, and (c) *REL*, and remaining erosion-free in seropositive RA subjects followed for 2 yrs

2a) Variables	Clinical model + *TRAF6*		
	OR	95% CI	P-value
Age at RA onset (every 5 yrs)	0.80	0.69, 0.93	0.002
Male gender	1.58	0.66, 3.8	0.30
RA duration (yrs)	0.87	0.83, 0.91	<0.0001
TRAF6	0.49	0.25, 0.96	0.04

2b) Variables	Clinical model + *IL2-IL21*		
	OR	95% CI	P-value
Age at RA onset (every 5 yrs)	0.75	0.61, 0.91	0.003
Male gender	2.1	0.65, 6.6	0.32
RA duration (yrs)	0.85	0.79, 0.91	<0.0001
IL2-IL21	0.15	0.03, 0.76	0.04

2c) Variables	Clinical model + *REL*		
	OR	95% CI	P-value
Age at RA onset (every 5 yrs)	0.79	0.68,0.92	0.002
Male gender	1.65	0.69, 3.9	0.26
RA duration (yrs)	0.87	0.82, 0.91	<0.0001
REL	0.61	0.37, 0.99	0.04

- No SNPs achieved significance after Bonferroni correction
- When disease duration limited to ≤10 years (n= 39 erosion free, 83 with erosions) none of the 3 SNPs were significant when added to the clinical model, however the direction of effect was similar

Limitations

- Sharp score for "erosion-free" has not been defined
- Power to detect an association limited by sample size
- Potential confounding, e.g., medications, disease duration
- Study conducted in a tertiary care center

Conclusions

- A subset of RA risk alleles may also play a role in determining erosion-free phenotype in seropositive RA
- Individuals carrying increasing copies of risk alleles for *TRAF6, IL2-IL21* or *REL,* were less likely to remain erosion-free than those who do not carry the risk alleles (not statistically significant)
- Further study of *REL* involved in osteoclast signaling may provide further insight into why some seropositive RA patients have erosive disease while others do not
- Larger studies in independent cohorts are needed to confirm these associations

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