POSTERS only

Genomics, genetic basis of disease and functional genomics

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RISK OF ACPA POSITIVITY BY MOTIF-BASED CLASSIFICATION OF HLA-DRB1 SHARED EPITOPE ALLELES IN RA

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Background: The shared epitope (SE) is the strongest known genetic risk factor for rheumatoid arthritis (RA) and is associated with an amino acid motif at positions 70-74 in HLA-DRB1. It is linked to anti-citrullinated protein antibody (ACPA) positivity, a specific serological marker for RA. In 2005, a new classification of HLA-DRB1 alleles was proposed, in which each allele is sorted into one of five classes (S1, S2, S3P, S3D, or X).¹ The method was subsequently validated for predicting risk of developing RA² and was described as “a major advance and a template for future studies.”³ However, there have been relatively few studies utilizing this classification.

Objectives: To characterize the prevalence of each SE genotype from the 2005 classification and their association with ACPA positivity in a cohort of individuals with RA.

Methods: Participants in FORWARD, The National Databank for Rheumatic Diseases, with RA and donated serum (collected 2010-2019) were analyzed to obtain ACPA status and high-resolution HLA-DRB1 type. Alleles were classified based on the presence (S2, S3P) or absence (S1, S3D, X; collectively L) of the SE motif, and individuals were classified by allele pair. Logistic regression models (adjusted for age, sex, and race/ethnicity) to determine risk of ACPA positivity by class were generated using L/L as the reference.

Results: Characteristics of the 855 participants at the time of sample collection are presented in Table 1. Overall, 67% of participants were SE positive and 51% were ACPA positive. Of the 1,710 total alleles, X was the most common (29%) followed by S3P (24%), S1 (18%), S2 (18%), and S3D (9%). Adjusted models showed that the risk of ACPA positivity was highest among those with the genotype S2/S3P, followed

Table 1. Characteristics of study population by SE status and allele count (mean [SD] or n [%]). Significance was assessed by Student's t-test or χ^2 test, as appropriate.

	SE negative		SE positive		P (SE- vs SE+)
	0 alleles n=286	All n=569	1 allele n=407	2 alleles n=162	
Age, years	57.4 (12.3)	58.1 (11.8)	58.0 (11.9)	58.5 (11.5)	0.42
RA duration, years	15.2 (12.8)	17.0 (13.9)	16.8 (14.1)	17.6 (13.4)	0.07
Female	259 (90.6)	500 (87.9)	359 (88.2)	141 (87.0)	0.24
White	260 (90.9)	525 (92.3)	372 (91.4)	153 (94.4)	0.49
History of smoking	117 (40.9)	223 (39.2)	166 (40.8)	57 (35.2)	0.63
RDCI, 0-9	2.4 (1.8)	2.0 (1.7)	2.1 (1.7)	1.9 (1.7)	<0.01
ACPA positive	74 (25.9)	365 (64.1)	241 (59.2)	124 (76.5)	<0.001
RF positive	84 (29.4)	333 (58.5)	219 (53.8)	114 (70.4)	<0.001
Pain VAS, 0-10	4.2 (2.7)	3.6 (2.7)	3.7 (2.6)	3.5 (2.9)	<0.01
Patient global severity, 0-10	4.0 (2.5)	3.3 (2.5)	3.4 (2.4)	3.1 (2.6)	<0.001
HAQ-II, 0-3	1.0 (0.7)	0.8 (0.6)	0.8 (0.6)	0.8 (0.6)	<0.001
csDMARD use	204 (71.3)	433 (76.1)	302 (74.2)	131 (80.9)	0.13
bDMARD use	165 (57.7)	351 (61.7)	244 (59.95)	107 (66.0)	0.26
Corticosteroid use	98 (34.3)	165 (29.0)	121 (29.7)	44 (27.2)	0.12

by S2/S2, S2/S3D, S2/X, S3P/S3D, S1/S2, S3P/S3P, S3P/X, and S1/S3P (Figure 1).

Figure 1. Risk of ACPA positivity by the motif-based classification and prevalence of SE by binary status, allele count, and class. The area within each circle is proportionate to the sample size of that group.

Conclusion: The ranking by risk of ACPA positivity among this RA cohort is similar to the order of risk for developing RA, as determined in the 2006 validation paper for this classification method. A notable trend among the classes with one SE positive allele is the consistent ranking of S3D as higher risk, X in the middle, and S1 as the lowest, suggesting a potential protective effect from S1 alleles. Future work should examine clinical associations with these allele classes, including disease progression and treatment effects.

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CLINICOGENETIC STUDY OF FIVE NOVEL SUSCEPTIBILITY LOCI FOR TAKAYASU ARTERITIS: SUSCEPTIBILITY LOCI IN THE IL12B AND PTK2B REGION, BUT NOT THE LILRA3, DUSP22, KLHL33 REGIONS, ARE ASSOCIATED WITH VASCULAR DAMAGE IN TAKAYASU ARTERITIS

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