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Letter

Rheumatoid Arthritis Known HLA Associations are Unlikely To Be Associated With Atopic Dermatitis

To the Editor:

Individuals with atopic dermatitis (AD) frequently have illnesses such as asthma and seasonal allergies. Recent studies have revealed associations between AD and rheumatoid arthritis (RA)[1,2]. For example, a study from Germany showed an increased risk of RA for those with AD (risk ratio 1.72, 95% CI 1.25–2.37). The study included a genetic evaluation and was not able to demonstrate that AD and RA shared known genetic risk using a genome-wide association study (GWAS) approach[1].

RA has an established and strong association with HLA polymorphisms that account for ~18% of the genetic risk of seropositive RA[3,4]. GWAS approaches do not optimally evaluate HLA genes[4,5]. HLA-DRβ1 amino acid residues located at positions 11,13, 71, and 74 are found in ~80% of those who have seropositive RA and represent the receptor phenotype associated with HLA-DRβ1 allelic variation[4,5]. Specifically, amino acids like valine (V; OR > 4.0 favoring RA), leucine (L; OR > 2.0), or serine (S; OR < 0.40) at position 11 can have profound effects on how the HLA receptor on T cells binds with antigen, potentially influencing the pathophysiology of RA[4]. In this letter, we report a detailed analysis of the known HLA RA-associated polymorphisms in a cohort of individuals with AD and a control group to assess whether HLA RA-associated polymorphisms are also associated with AD, thereby enhancing our understanding of the relationship between RA and AD.

Subjects for this study were from either the Genetics of Atopic Dermatitis or the Pediatric Eczema Elective Registry (PEER) cohorts[6]. Cases had a history and an examination consistent with AD, and controls had no AD by history and examination. There were no enrollment conditions for other illnesses. All subjects provided informed consent prior to providing DNA sample. This study was approved by the University of Pennsylvania Institutional Review Board (protocol approval #809924).

Most prior investigations of RA and HLA focused on subjects of European ancestry, as did we because HLA varies by ancestry[4]. The 11 *HLA* genes (*-A*, *-B*, *-C*, *-DRB1*, *-DRB3/4/5*, *-DQA1*, *-DQB1*, *-DPA1*, and *-DPB1*) were sequenced using targeted, amplicon-based, next-generation sequencing (NGS) with Omixon Holotype HLA V2 kits. Results are reported as allelic frequencies and OR with 95% CI. Statistical analyses were conducted using Stata Version 16.1 (StataCorp). We focused on previously reported HLA RA genetic risk associations[5].

The cohort consisted of 631 individuals, including 216 controls and 415 cases. Of these individuals, 53.1% were female. The clinical characteristics of the cohort are presented in Table 1. Of the RA risk alleles, only 3 had an allelic frequency ≥ 0.05 in the AD group, and none of the HLA-DRB1 risk alleles were associated with AD as compared to the controls (Table 2). None of the HLA-DRB1 variants compared to controls were statistically significant or had effect estimates similar to previous reports for RA subjects[5]. None of the RA risk residue haplotypes were associated with AD as compared to the controls (Table 2) and the previously reported consistency of effect of the residues was not observed[5]. With respect to RA risk, adjusting for -B, -DPB, and -DRB1 had no effect on the risk effect estimates. The -DRB1 residues thought to be associated with the highest risk of RA (valine position 11) and most protective (serine position 11) were not associated with AD as compared with controls (OR 0.88, 95% CI 0.59–1.32, and OR 0.88, 95% CI 0.69–1.12, respectively)[5].

Individuals with AD have been shown to have disorders in both the skin barrier and immunologic functioning. The *FLG* gene (filaggrin), which produces a protein important for skin barrier function as a loss of function (LOF) variant, is associated with 2-times and 4-times increased risk of AD[7]. Interestingly, FLG is an anticitrullinated cyclic peptide antibody (anti-CCP2), which are highly prevalent (~80%) in seropositive RA[4,8,9]. However, FLG LOF variants are not associated with RA[10]. The role of anti-CCP2 and how they may relate to the 2 diseases is not clear, but the fact that FLG LOF mutations confer high risk for AD and are unrelated to RA risk further suggests that the genetics of these 2 diseases are quite distinct.

In our study, by using high-resolution (2-field) HLA typing by NGS, we

Table 2. Allelic associations (OR and 95% CI) comparing atopic dermatitis (AD) to controls and allelic frequencies (AF) for RA HLA-DRB1 risk alleles.

Allele	OR (95% CI)	AF AD (95% CI)	AF Controls (95% CI)
DRB1*01:01	**0.76 (0.50–1.14)**	**0.07 (0.05–0.09)**	**0.09 (0.07–0.12)**
DRB1*01:02	0.92 (0.40–2.12)	0.02 (0.01–0.03)	0.02 (0.01–0.04)
DRB1*04:01	**0.90 (0.57–1.43)**	**0.07 (0.05–0.09)**	**0.08 (0.05–0.11)**
DRB1*04:02	0.43 (0.13–1.41)	0.01 (0.00–0.01)	0.01 (0.01–0.03)
DRB1*04:03	0.52 (0.10–2.58)	0.00 (0.00–0.01)	0.01 (0.00–0.02)
DRB1*04:04	**1.81 (0.93–3.53)**	**0.05 (0.03–0.07)**	**0.03 (0.01–0.05)**
DRB1*04:05	0.69 (0.15–3.12)	0.00 (0.00–0.01)	0.01 (0.00–0.02)
DRB1*04:07	3.69 (0.45–30.18)	0.01 (0.00–0.02)	0.00 (0.00–0.01)
DRB1*04:08^	2.01 (0.22–∞)	0.00 (0.00–0.01)	0.00 (0.00–0.01)
DRB1*09:01	2.30 (0.65–8.14)	0.02 (0.01–0.03)	0.01 (0.00–0.02)
DRB1*10:01	0.83 (0.27–2.57)	0.01 (0.00–0.02)	0.01 (0.00–0.03)
DRB1*16:01	1.04 (0.46–2.37)	0.02 (0.01–0.03)	0.02 (0.01–0.04)
SE	**1.19 (0.83–1.71)**	**0.27 (0.23–0.32)**	**0.24 (0.18–0.30)**

The highest risk alleles in RA include -04:01, -04:10, -04:08, -04:05, -04:04, -04:06, -04:11, -04:15, and -10:01, and are also referred to as shared epitope (SE).[5] AF of ≥ 0.05 in bold. ^ Exact logistic regression. No $P < 0.05$.

Table 1. Basic clinical information about the cohort with respect to those with and without atopic dermatitis (AD), and with and without the shared epitope (SE; i.e., RA HLA-DRB1 risk alleles 04:01, -04:10, -04:08, -04:05, -04:04, -04:06, -04:11, -04:15, and -10:01[5]).

	AD, n = 415	No AD, n = 216	SE+, n = 165	SE–, n = 466
History of AD	100 (415)	0 (0)^	69.1 (114)	64.6 (301)
History of asthma	52.8 (219)	6 (2.8)^	35.8 (59)	35.6 (166)
History of seasonal allergies	61.7 (256)	5.1 (11)^	41.8 (69)	42.5 (198)
AD disease onset, yrs, mean (SD)	9.19 (1.83)	NA	9.19 (2.30)*	9.20 (3.00)*
AD patient-reported outcome[6], median	3 (limited control)	NA	3* (limited control)	3* (limited control)

Data presented as percentage (n) unless otherwise specified. * Only among those with AD. ^ $P < 0.0001$. NA: not applicable; RA: rheumatoid arthritis.

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Table 3. Amino acid residues at location 11, 13, 71, and 74 for HLA-DRB1 known to increase risk of RA[5].

Residues (11/13/71/74)	OR (95% CI)	CF Controls, n = 216	CF AD, n = 415	DRB1 Allele
		HLA-DRB1		
VHKA	0.90 (0.57–1.43)	0.08 (0.05–0.10)	0.07 (0.05–0.09)	-04:01
VHRA	1.59 (0.93–2.68)	0.04 (0.03–0.07)	0.07 (0.05–0.09)	-04:10, -04:08, -04:05, -04:04, -04:06, -04:11, -04:15, -10:01
LFRA	0.78 (0.53–1.14)	0.11 (0.08–0.15)	0.09 (0.07–0.11)	-01:01, -01:02
PRRA	0.85 (0.39–1.80)	0.02 (0.01–0.04)	0.02 (0.01–0.03)	-16:02
VHRE	1.44 (0.45–4.59)	0.01 (0.00–0.02)	0.01 (0.01–0.02)	-04:03, -04:07, -04:92
NFRE	2.30 (0.65–8.14)	0.01 (0.00–0.02)	0.02 (0.01–0.03)	-09:01
VHEA	0.43 (0.13–1.42)	0.01 (0.00–0.03)	0.01 (0.00–0.01)	-04:02
SSKA	0.86 (0.31–2.41)	0.01 (0.00–0.03)	0.01 (0.00–0.02)	-13:03
PRAA	1.10 (0.79–1.52)	0.14 (0.10–0.17)	0.15 (0.12–0.17)	-15:01, -15:02, -15:03
GYRQ	1.17 (0.80–1.70)	0.11 (0.08–0.14)	0.12 (0.10–0.14)	-07:01
SSRA	1.10 (0.80–1.59)	0.13 (0.10–0.16)	0.13 (0.11–0.15)	-11:01, -11:04, -12:01, -12:02
SSRE	0.73 (0.36–1.48)	0.03 (0.02–0.05)	0.02 (0.01–0.04)	-14:01, -14:54, -14:04
SGRL	0.83 (0.27–2.57)	0.01 (0.00–0.03)	0.01 (0.00–0.02)	-01:03
SSKR	0.82 (0.57–1.19)	0.12 (0.09–0.16)	0.10 (0.08–0.13)	-03:01, -03:02
SSEA	1.03 (0.71–1.50)	0.11 (0.08–0.14)	0.11 (0.09–0.14)	-13:05, -11:02, -11:03, -13:01, -13:02, -11:11, -13:15
		HLA -B		
D	1.08 (0.74–1.57)	0.10 (0.07–0.13)	0.11 (0.09–0.13)	-08:01
		HLA-DPB		
F	1.09 (0.90–1.32)	0.46 (0.41–0.51)	0.49 (0.46–0.52)	-04:02, -16:01, -02:01, -34:01, -40:01, -106:01, -23:01, -51:01, -584:01, -19:01, -416:01, -105:01, -02:02, -05:01, -04:01

OR reported for AD risk as compared to controls. Residue CF reported with 95% CI. HLA-DRB1 alleles that contribute to the residue are also listed. Additional risk variants are reported for position 9 for HLA-B and position 9 HLA-DPB1. Amino acids are reported as accepted one letter code. No $P < 0.05$. Amino acids in boldface: V (valine); L (leucine); S (serine). AD: atopic dermatitis; CF: composite frequency; RA: rheumatoid arthritis.

showed that AD is very unlikely to be associated with RA HLA risk alleles or high-risk HLA receptor variation. This lack of common HLA risk factors participating in both diseases argues for different genetic pathophysiologies for RA and AD. Assuming that AD is associated with an increased risk for RA as reported[1,2], and this risk has a genetic basis, the genetic risk still needs to be discovered. However, it is also possible that associations with RA and AD are due to disease misclassification or selection bias known to be present in studies using administrative records. Before concluding that there is an association of AD with seropositive RA or any joint disease, future prospective studies evaluating joint pathology in those with AD are recommended.

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D.J. Margolis is or recently has been a consultant for Pfizer, Leo, and Sanofi with respect to studies of atopic dermatitis and serves on an advisory board for the National Eczema Association. D.S. Monos is Chair of the Scientific Advisory Board of Omixon, and owns options in and receives royalties from Omixon.

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