HLA Associations in a Cohort of Children With Juvenile Idiopathic Arthritis With and Without Uveitis

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PURPOSE. Juvenile idiopathic arthritis (JIA)-associated uveitis can lead to ocular complications and vision loss. Alleles *HLA-DRB1*08*, **11*, and **13* are risk alleles for JIA, whereas *HLA-DRB1*11* and **13* alleles increase uveitis susceptibility. We examined the association of common HLA-DRB1 alleles in children with JIA alone and JIA-associated uveitis.

METHODS. High-resolution HLA-DRB1 genotyping was performed in 107 children with oligoarticular and polyarticular rheumatoid factor (RF) negative JIA and 373 non-Hispanic white controls. Children with JIA alone and JIA-associated uveitis were of similar race, ethnicity, sex, and age at arthritis diagnosis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

RESULTS. There were 47 children with JIA-associated uveitis and 60 with JIA alone. Compared to controls, only children with JIA-associated uveitis had increased odds of carriage of *HLA-DRB1*11* (OR, 2.2 [95% CI, 1.1-4.3], $P = 0.023$). There also was increased carriage of *HLA-DRB1*08* and **13* (OR, 12.6 [95% CI, 2.0-77.8], $P = 0.011$). Compared to controls and children with JIA alone, those with JIA-associated uveitis had increased odds of carriage of *HLA-DRB1*11* and **13* (OR, 9 [95% CI, 2.8-29.0], $P < 0.0001$ and OR, 8.6 [95% CI, 1.0-74.4], $P = 0.042$), respectively.

CONCLUSIONS. We report the novel finding that carriage of *HLA-DRB1*11* and **13* appears to increase the risk of uveitis in children with JIA.

Keywords: uveitis, HLA, juvenile idiopathic arthritis

Uveitis is the most common extraarticular manifestation of juvenile idiopathic arthritis (JIA) and can increase a child's risk for ocular complications and permanent vision loss. Juvenile idiopathic arthritis is a chronic childhood arthritis of unknown etiology consisting of 7 categories that differ in their risk for uveitis development.¹ Children with oligoarticular and polyarticular rheumatoid factor (RF)-negative JIA are considered at highest risk. Clinical risk factors for uveitis are well-established, but less extensive investigation has been conducted on genetic associations.

Studies in JIA-associated uveitis have focused on *HLA-DRB1* alleles in children with oligoarticular and polyarticular RF-negative JIA because of their increased risk for uveitis development. In JIA, associations have been confirmed with HLA and non-HLA genetic variants.^{2,3} These include HLA Class II genes, such as *HLA-DRB1*13:01;DQA1*01:03;DQB1*06:03* in oligoarticular JIA, and *DRB1*08:01;DQA1*04:00;DQB1*04:02* and *DRB1*11:03/1104;DQA1*05:00;DQB1*03:01* haplotypes in polyarticular RF negative JIA.⁴ There also are reports of increased arthritis risk in adults with rheumatoid arthritis and in children with RF-positive JIA with certain HLA genetic combinations, such as *HLA-DRB1*04:01/04:04*.^{5,6} Principal components analysis of HLA class I and II loci has shown the clustering of young onset oligoarticular and RF-negative polyarticular JIA

patients.⁴ These children are at greatest risk for uveitis development, hence the focus of our study.

Our objective was to explore the association of known *HLA-DRB1* alleles in a cohort of children with oligoarticular and polyarticular JIA who develop uveitis. We also investigated whether there is a synergistic effect of risk variants that predispose to the development of two autoimmune diseases – arthritis and uveitis. We sought to determine if children with JIA-associated uveitis demonstrate differences in *HLA-DRB1* alleles or allele combinations compared to children with JIA alone. Recently, specific and shared genetic associations were noted in individuals with acute anterior uveitis and ankylosing spondylitis, suggesting distinct genetic profiles in individuals with arthritis who develop uveitis.⁷ Although earlier studies used old terminology when reporting HLA data, for uniformity, we will attempt to use the new nomenclature in our study and discussion when possible. However, we are not always able to determine whether *HLA-DR5* refers to *DRB1*11* or *DRB1*12*.

PATIENTS AND METHODS

Subjects

We enrolled 107 non-Hispanic white (NHW) children with oligoarticular or polyarticular RF negative JIA (60 with JIA alone

TABLE 1. HLA Associations of Children With Juvenile Idiopathic Arthritis Alone, Juvenile Idiopathic Arthritis-Associated Uveitis, and Controls

HLA Configuration	JIA Alone, <i>n</i> = 60, vs. Controls, <i>n</i> = 373	JIA-Associated Uveitis, <i>n</i> = 47, vs. Controls, <i>n</i> = 373	JIA Alone, <i>n</i> = 60, vs. JIA-Associated Uveitis, <i>n</i> = 47
<i>DRB1</i> *08	23.3% vs. 5.1% OR 5.6 (2.7–12.1)* <i>P</i> < 0.0001†	34% vs. 5.1% OR 9.6 (4.5–20.6) <i>P</i> < 0.0001†	23.3% vs. 34% OR 1.7 (0.7–4.0) <i>P</i> = NS
<i>DRB1</i> *11	20% vs. 16.4% OR 1.3 (0.6–2.5) <i>P</i> = NS	29.8% vs. 16.4% OR 2.2 (1.1–4.3) <i>P</i> = 0.023	20% vs. 29.8% OR 1.7 (0.7–4.1) <i>P</i> = NS
<i>DRB1</i> *13	36.7% vs. 23.1% OR 1.9 (1.1–3.4) <i>P</i> = 0.023	40.4% vs. 23.1% OR = 2.3 (1.2–4.2) <i>P</i> = 0.010	36.7% vs. 40.4% OR 1.2 (0.5–2.6) <i>P</i> = NS
<i>DRB1</i> *08/11	5% vs. 1.1% OR 4.8 (1.05–21.9) <i>P</i> = 0.059	4.3% vs. 1.1% OR 4.1 (0.7–23.0) <i>P</i> = NS	5% vs. 4.3% OR 0.84 (0.1–5.3) <i>P</i> = NS
<i>DRB1</i> *08/13	1.7% vs. 0.5% OR 3.1 (0.3–35.2) <i>P</i> = NS	6.4% vs. 0.5% OR 12.6 (2.0–77.8) <i>P</i> = 0.011	1.7% vs. 6.4% OR 4.0 (0.4–40.0) <i>P</i> = NS
<i>DRB1</i> *11/13	1.7% vs. 1.6% OR 1.04 (0.1–8.8) <i>P</i> = NS	12.8% vs. 1.6% OR 9.0 (2.8–29.0) <i>P</i> < 0.0001†	1.7% vs. 12.8% OR 8.6 (1.0–74.4) <i>P</i> = 0.042 (exact)

NS, not significant.

* OR (95% CI).

† Statistically significant after adjusting for multiple comparisons.

and 47 with JIA-associated uveitis). We only included children who were diagnosed with JIA for at least 4 years since >80% of children who have uveitis do so within that timeframe.^{8,9} There were no statistically significant differences in JIA category, sex, race, ethnicity, or age at arthritis diagnosis between subjects with and without uveitis (data not shown). The healthy control group consisted of 373 healthy NHW individuals from the University of Utah and Cincinnati Children's Hospital. Some of the controls were included in a previous study.⁴ Approval from the institutional review boards at each institution was obtained. We followed the tenets of the Declaration of Helsinki and informed consent was obtained after we explained the nature of the study.

HLA-DRB1 Genotyping and Classification

We extracted DNA from peripheral blood mononuclear cells per established protocols and performed high-resolution sequence-based *HLA-DRB1* genotyping on all patients and controls. We only considered *HLA-DRB1**08, *11, and *13 as risk alleles as these are strongly associated with JIA and have been reported in JIA-associated uveitis. Our analysis was limited to two digit HLA resolution because of the modest sample size.

Statistical Analysis

Statistical analysis was conducted using SAS v 9.3 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was assessed at the 0.05 level unless otherwise noted. Descriptive statistics were calculated for all variables of interest and include means and standard deviations or counts and percentages when appropriate. We compared the frequencies of *HLA-DRB1* alleles between children with JIA alone and control subjects, children with JIA-associated uveitis and control subjects, and children with JIA alone and JIA-associated uveitis using χ^2 or Fisher's exact tests as appropriate. Odds ratios (ORs) and 95% confidence intervals (95% CI) were

calculated. We compared children with JIA-associated uveitis to controls to determine if there were initial differences in HLA risk alleles before comparing to children with JIA alone. Likewise, although most children with JIA will suffer uveitis within the first 4 years of their JIA diagnosis, we were unable to account for delayed uveitis onset and subclinical disease.

To control for multiple comparisons, we applied a Bonferroni correction using an adjusted significance level of $0.05/9 = 0.006$. This adjustment was chosen because each primary HLA allele configuration (*HLA-DRB1**08, *HLA-DRB1**11, *HLA-DRB1**13) was tested three times and there were three planned pairwise comparisons for each configuration (JIA alone versus control, JIA-associated uveitis versus control, and JIA alone versus JIA-associated uveitis).

RESULTS

There were 107 NHW children with oligoarticular or polyarticular RF-negative JIA. Median age at JIA diagnosis was 3.5 years (2.2–5.5) for those with JIA and 3.1 years (2.0–4.0) for those with JIA-associated uveitis. Approximately 75% of children had oligoarticular JIA and 25% had polyarticular RF-negative JIA. Of children with JIA alone 12% (7/60) were ANA positive versus 62% (29/47) with JIA-associated uveitis, which was significantly different ($P < 0.0001$). In children with uveitis, the median age at uveitis diagnosis was 4.0 years (interquartile ratio [IQR] 2.8–5.6) with a median duration of arthritis before uveitis of 1.3 years (IQR 0.1–3.5). Most had bilateral disease (79%) and several ocular complications.

We first examined carriage of single risk alleles. On examining *HLA-DRB1* alleles in 60 children with JIA alone and 373 control subjects, we confirmed a significant association between JIA and *HLA-DRB1**08 (23.3% JIA alone versus 5.1% controls; OR, 5.6 [95% CI, 2.7–12.1], $P < 0.0001$) and *DRB1**13 (36.7% JIA alone versus 23.1% controls; OR, 1.9 [95% CI, 1.1–3.4], $P = 0.023$; Table 1). On examining *HLA-DRB1* alleles in 47 children with JIA-associated uveitis and 373 controls, significant associations were noted with *HLA-*

TABLE 2. Genetic Association Studies in Children With JIA-Associated Uveitis Compared to Controls or Children With JIA

Author	JIA-Associated Uveitis, N	JIA Sub-Type	JIA Alone, N	Controls, N	HLA-DR Association*	Other Associations*	Genetic Combinations*
Glass et al. ¹⁸	24	Oligoarticular	21	283	HLA-DRw5 OR 8.3 HLA-DRw8 OR 4.3		HLA-DRw5 and ANA†
Miller et al. ¹⁶	38	Oligoarticular		239 (family)	HLA-DR5 RR: 3.52‡ HLA-DRw8 RR 3.94‡ HLA-DRI, HLA-DR4, HLA-DR7 Protective	HLA-A2, HLA-Bw44, HLA-Bw16, HLA-Bw35, HLA-Cw4, MT2	HLA-Bw44, HLA-Cw4, HLA-DR5 RR 20.77‡ HLA-Bw35, HLA-Cw4, HLA-DR5 RR 9.23‡ HLA-DR5 and HLA-DPw2.1, but no HLA-DRI - 75% cumulative risk HLA-DR5 and HLA-DRw8 cumulative risk 70.8% HLA-DRB1*11:04 and HLA-DPB1*02:01 OR 7.77** HLA-DRB1*11:04 PLUS* HLA-DRw52, HLA-DRB1*08:01, HLA-DRB1*13:01, HLA-A2
Giannini et al. ¹⁹	70	Oligoarticular	91		HLA-DR5 OR 3.51 HLA-DRI OR 0.19	HLA-DPw2.1	
Melin-Aldana et al. ²⁰	61	Oligoarticular	69	218	HLA-DRB1*11:04 OR 3.45† HLA-DRI OR 0.18†	HLA-DQA1*01:01 Protective	
Malagon et al. ¹⁷	72	Oligoarticular	77		HLA-DR5 OR 3.19† HLA-DRI OR 0.22† HLA-DRw8 NS*† HLA-DRB1*01:01 Protective	HLA-DQA1*01:01, HLA-DQB1*05:01 Protective	
Ploski et al. ²⁸	125	Oligoarticular and polyarticular rheumatoid factor (-)	131	181	HLA-DRB1*01 Protective HLA-DRB1*11 NS*		
Haas et al. ²⁴	80	Oligoarticular	120	365	HLA-DR5 NS*		
Hall et al. ²⁵	84	Oligoarticular	74	192	HLA-DR5 NS*	HLA-A2, HLA-Bw62 HLA-B44 Protective HLA-A19, HLA-B22, HLA-DR2	ANA and HLA-DR5 ANA and HLA-A2
Zulian et al. ²¹	130	Oligoarticular	186		HLA-DRI OR 0.27† HLA-DR5 or HLA-DR8 NS*		
Zeggini et al. ²³	31	Oligoarticular	99 228 replication ?subtypes	130 healthy parents of cases	HLA-DRB1*13 OR 3.4 in replication	HLA-A, HLA-B, or SNPs for TNFalpha, HLA-E and DIF-2 NS*	

TABLE 2. Continued

Author	JIA-Associated Uveitis, N	JIA Sub-type	JIA Alone, N	Controls, N	HLA-DR Association*	Other Associations*	Genetic Combinations*
Grassi et al. ²²	62	Oligoarticular, polyarticular and systemic onset	247		<i>HLA-DRB1*11</i> OR 3.47, 95% CI 1.16–7.47, <i>P</i> = 0.001† <i>HLA-DRB1*08</i> OR 0.26, 95% CI 0.12–0.57, <i>P</i> = 0.001‡	<i>HLA-A19</i> , <i>HLA-B22</i> , <i>HLA-B27</i> , <i>HLA-DR1</i> , <i>HLA-DR9</i> NS*	

* Associations reported in terminology used in their respective studies.

† Compared to JIA.

‡ Compared to controls.

*DRB1*08* (34% JIA-associated uveitis versus 5.1% controls; OR, 9.6 [95% CI, 4.5–20.6]; *P* < 0.0001), *HLA-DRB1*11* (29.8% JIA-associated uveitis versus 16.4% controls; OR, 2.2 [95% CI, 1.1–4.3]; *P* = 0.023) and *HLA-DRB1*13* (40.4% JIA-associated uveitis versus 23.1% controls; OR, 2.3 [95% CI, 1.2–4.2]; *P* = 0.010). There were no differences in the frequencies of *HLA-DRB1*08*, **11*, or **13* alleles between children with JIA and those with JIA-associated uveitis.

We next determined if the risk of JIA-associated uveitis was increased in children who carried two risk alleles. Of note, we did not find any children who were homozygous for *HLA-DRB1*08*, **11*, or **13*. Carriage of two risk HLA *DRB1* alleles was not significantly different between children with JIA alone compared to healthy controls. However, carriage of two risk HLA *DRB1* alleles was significantly higher among children with JIA-associated uveitis compared to healthy controls: (1) *HLA-DRB1*11* and *DRB1*13* (12.8% JIA-associated uveitis versus 1.6% controls; OR, 9 [95% CI, 2.8–29.0]; *P* < 0.0001) and (2) *HLA-DRB1*08* and *DRB1*13* (6.4% JIA-associated uveitis versus 0.5% controls; OR, 12.6 [95% CI, 2.0–77.8], *P* = 0.011).

When comparing children with JIA-associated uveitis and JIA alone, we again noted a significant association with *HLA-DRB1*11* and *DRB1*13* (12.7% JIA-associated uveitis versus 1.7% JIA alone, OR = 8.6 [95% CI, 1.0–74.4], *P* = 0.042). We then determined that carriage of either *HLA-DRB1*08* and *DRB1*13* (6.3% JIA-associated uveitis versus 1.6% JIA alone) or *HLA-DRB1*11* and *DRB1*13* (12.8% JIA-associated uveitis versus 1.6% JIA alone) had an increased OR of 6.9 [95% CI, 1.4–33.5], *P* = 0.017.

After adjusting our significance level to 0.006 to control for multiple comparisons, an increased odds of JIA-associated uveitis remained statistically significant for *HLA-DRB1*11/*13* compared to controls. However, compared to JIA alone, the clinically significant increased odds of JIA-associated uveitis observed for *HLA-DRB1*11/13* (OR = 8.6) was no longer statistically significant. This also was true when comparing the frequency of *HLA-DRB1*11*, *HLA-DRB1*13*, and *HLA-DRB1*08/13* among JIA-associated uveitis and control patients, and when comparing frequency of *HLA-DRB1*13* among JIA-alone and controls. *HLA-DRB1*08* remained statistically significant for JIA alone and JIA-associated uveitis compared to controls.

DISCUSSION

Alleles *HLA-DRB1* have been associated with JIA, and *HLA-DRB1*11* and **13* alleles increase susceptibility to uveitis. We confirm associations between JIA, JIA-associated uveitis and *HLA-DRB1*08*, **11*, and **13*. We newly describe, to our knowledge, an association between uveitis and carriage of two *HLA-DRB1* risk alleles, *HLA-DRB1*11/*13* or **08/*13*, compared to children with JIA alone, suggesting a possible gene dosage effect. Our findings are novel given that we describe the combination of two risk alleles in a population of children with JIA-associated uveitis compared to JIA alone and controls, whose size is comparable to earlier studies.

As reviewed elsewhere, several HLA associations have been confirmed in chronic noninfectious uveitis, such as in acute anterior nongranulomatous uveitis (*HLA-B27*), Vogt-Koyanagi-Harada's disease (*HLA-DRB1*04*), Birdshot retinochoroidopathy (*HLA-A29*), and intermediate uveitis (*HLA-DR2*, *HLA-DR15*, *HLA-B8*, and *HLA-B51*).¹⁰ Distinct associations were noted recently in adults with acute anterior uveitis with and without ankylosing spondylitis.⁷ However, less extensive work has been conducted in children with JIA-associated uveitis. Family and sibling studies have supported a genetic association, but not an increased sibling recurrence ratio in

uveitis.^{11–14} Most investigations to date focus primarily on the HLA region.¹⁵

An approximately 3-fold risk for uveitis has been attributed to *HLA-DR5*^{16–20} (which subsequently has been split into *DRB1*11* and *DRB1*12*), and a protective effect of *HLA-DR1* (Table 2).^{16–25} Examination of *DRB1*11* and *DRB1*12* individually in children with JIA and JIA-associated uveitis has shown an increased risk for uveitis in *HLA-DRB1*11:04* in linkage equilibrium with *HLA-DQA1*05:01* and *HLA-DQB1*03:01*.^{20,22} Our study confirmed the association of uveitis with *HLA-DRB1*11* and **13* in children with JIA.

Multiple risk alleles have been reported to influence phenotype, particularly related to early JIA susceptibility.²⁶ It is unclear whether confirmed HLA variants predispose to arthritis and uveitis separately, or if there are synergistic effects related to eye disease. Our data suggest a potential gene dosage effect in children with JIA-associated uveitis when compared to those with JIA alone and controls. This was similar to a study of 13 children with JIA who carried *DRB1*11:04* and *DPB1*02:01* alleles, wherein 11 also had uveitis with an increased odds of 7.8-fold.²⁰ Similarly, 8 of 18 children with JIA-associated uveitis and *HLA-DRB1*11:04* additionally had either *HLA-DRB1*11:04* or *HLA-DRB1*13:01*. This combination was not found in 12 controls. Haas et al.²⁴ noted that children with uveitis had three associated alleles, specifically, the *HLA-DRB1* allele on haplotypes and *DPB1*02:01* (RR 3.11), compared to those without uveitis.²⁵ Another group noted that, 5 years after JIA onset, children with (1) *HLA-DR5* and *HLA-DP2.1* positivity but *HLA-DRB1*01* negativity, or (2) *HLA-DR5* and *HLA-DRB1*08* positivity had a cumulative risk for uveitis of approximately 75%.¹⁹ We show that when comparing children with JIA-associated uveitis to those with JIA alone or to controls, a combination of multiple *HLA-DRB1* alleles may predispose to uveitis and, hence, influence phenotype. Further elucidation on the complex pathogenesis of JIA-associated uveitis, specifically with regards to the genetic predisposition is important.

There were several limitations to our study. Due to our small sample size, we were unable to conduct tests of heterogeneity to determine strengths of associations compared to controls. We limited our chosen loci to those previously reported in the literature to validate in our cohort. We felt that given our small numbers, two digit resolution was appropriate, and was also similar to previous reports. However, despite our small cohort, our finding that the combination of the carriage of *HLA-DRB1*11* and *DRB1*13* was rare as it was only observed in 6/373 controls and 1 child with JIA compared to 6/47 children with JIA-associated uveitis.

Our controls were enrolled in Utah and Cincinnati, and our cases were enrolled in Utah and Atlanta. However, our controls have been genotyped using different platforms in previous studies and have not demonstrated population stratification. This could be a potential limitation.^{3,27}

In summary, our preliminary work shows that children with JIA and JIA-associated uveitis share *HLA-DRB1*-associated alleles, but children with certain combinations of risk alleles may have a higher predilection for developing uveitis. We newly showed, to our knowledge, that combinations of *HLA-DRB1* genes in children with JIA may predispose to uveitis development. Understanding the genetic risk for uveitis may lead to improvements in the screening algorithm for patients with JIA.

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