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HLA-DRB1*15:01 Is Associated and Linked With Kawasaki Disease, With DRB1*14:01 Conferring Risk to Coronary Artery Lesions: Case-Control and Family-Based Studies

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ABSTRACT

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is a leading cause of vasculitis in children aged < 5 years. The HLA complex has been investigated for its association with KD since 1978 without conclusive results due to limitations such as small sample sizes. This study aimed to evaluate the associations and genetic linkage between HLA-DRB1 and KD, as well as its complications. The case-control and family-based studies enrolled 795 patients with KD and 946 healthy controls. Of the 795 patients, 180 trios were included. Genotypes of HLA-DRB1 were identified by sequence-based typing according to the International ImmunoGeneTics database. Allele frequencies were calculated using PyPop 7.0. The transmission/disequilibrium test (TDT) was used to verify the genetic linkage between HLA-DRB1 and KD. HLA-DRB1*15:01 was significantly associated with KD (OR, 1.44, P =0.03) and with KD without CALs (OR=1.46, P =0.04). HLA-DRB1*14:01 was a risk factor for KD with CALs (OR=2.47, P =0.004) whereas HLA-DRB1*12:02 was a protective factor against CALs (OR=0.49, P =0.01). In the family-based study, HLA-DRB1*15:01 demonstrated significant overtransmission to KD patients (OR=3.35; 95% CI, 2.20–5.78; P =1.19E-06) and to KD patients without CALs (OR=4.42; 95% CI, 2.59–10.08; P =6.24E-06). The overtransmission remained significant in male KD patients (OR=2.81; 95% CI, 1.68–5.58; P =0.003), and in male KD patients without CALs (OR=3.22; 95% CI, 1.69–8.84; P =0.02). Our study identified significant associations between HLA-DRB1*15:01, *14:01, and *12:02 with KD. The association between HLA-DRB1*15:01 and KD was further verified by TDT, indicating a genetic linkage between the HLA-DRB1 locus and KD susceptibility.

1 | Introduction

Kawasaki disease (KD, ICD-10CM: M30.3; OMIM 611775), or mucocutaneous lymph node syndrome, is a systemic vasculitis

characterised by inflammation of blood vessels, mostly affecting children aged < 5 years [1, 2]. The latest incidence of KD in Japan and Korea is > 200 per 100,000 which is the highest worldwide. Our country ranks 3rd after Japan and Korea as > 50

Abbreviations: CALs, coronary artery lesions; CI, confidential interval; KD, Kawasaki disease; OR, odds ratio; TDT, transmission/disequilibrium test.

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per 1,000,000 children <5 years old [3]. Clinical presentation includes prolonged fever lasting over 5 days, insensitivity to antibiotic treatment, strawberry tongue, lymphadenopathy, swelling and erythema of hands and feet, bilateral conjunctivitis, polymorphous skin rash, oral inflammation, and coronary artery lesions (CALs) [4]. The most serious complication involves CALs including dilatation and aneurysms, which develop in approximately 15%–25% of untreated patients [4]. Intravenous immunoglobulin (IVIG), aspirin, and steroids are the treatments for KD. Even with IVIG therapy, CALs may still develop in around 5% of patients [5]. Currently, KD is the leading cause of acquired heart disease in children [6, 7].

HLA plays a crucial role in the immune system and its association with KD has been investigated since 1978 [8]. The HLA subtypes associated with KD vary according to ethnicity [9]. HLA-B54 and -Bw22 have been reported in Japanese populations and -Bw51 in Caucasian and Jewish groups [8, 10, 11]. Although becoming not significant after application of corrections for multiple comparisons, HLA-B35, -B75, and -Cw09 were reportedly associated with KD; and *HLA-DRB1*11* and *-DRB1*09* with CALs in Korean KD patients [12]. We also found HLA-MICA A4 significantly associated with CALs, which was later validated by a genome-wide association case-control study in another Taiwanese population [13, 14]. Ye et al. confirmed the involvement of CD25, CD69 and HLA-DR on CD4⁺ and CD8⁺ T cells in KD pathogenesis. The percentage of CD8⁺ HLA-DR⁺ T cells serves for predicting IVIG responsiveness [15]. However, these previous studies on the associations between HLA and KD have limitations, such as small sample sizes, low genotyping resolution, and limited variant coverage. Additionally, many found no associations, potentially owing to these methodological constraints [12, 14, 16–20]. Based on these previous studies, HLA-DRB1 may play an important role in KD susceptibility and warrant exploration in a large population. Therefore, we performed this study to evaluate the associations of HLA-DRB1 with KD susceptibility and CALs, and the allele transmission analysed by the transmission/disequilibrium test (TDT) in a large Taiwanese population.

2 | Material and Methods

2.1 | Subjects

This case-control study included 795 patients with KD (476 males and 319 females). Of these, 225 (159 males and 66 females) had CALs; 180 (64 with CALs; 48 males) had their parents forming trios for the family-based study using the TDT. The

diagnosis of KD was based on the American Heart Association diagnostic criteria for KD [4]. Treatment regimens included aspirin, IVIG, and/or steroids. All patients underwent echocardiography during the acute stage and before discharge. CALs were defined as coronary arteries with a diameter of ≥ 3 mm in children aged < 5 years or ≥ 4 mm in children aged ≥ 5 years or with a border-to-border inner diameter of > 1.5 times that of an adjacent segment. Echocardiograms were interpreted by a paediatric cardiologist (Ming-Ren Chen). We recruited 946 healthy individuals (489 males and 457 females) free from KD who served as the control group. They were from among hospital personnel or individuals undergoing routine health examinations or minor surgery. None had a history of asthma, diabetes, or autoimmune diseases. Ages were recorded for 734 (12.3 ± 10.2 , 0.1–59.6 years), but the remaining 212 were only noted to be adults (Table 1). All patients and controls were ethnic Chinese living in Taiwan [21]. This study was followed by the declaration of Helsinki and approved by the Institute Review Board of MacKay Memorial Hospital (18MMHIS185, 21MMHIS123e, 21MMHIS363e, and 24MMHIS540e).

2.2 | HLA Genotyping and Identification

Genomic DNA for HLA typing was extracted from whole blood samples of all participants following the manufacturer's guidelines (Qiagen, Maryland, MD, USA). The DNA specimens were genotyped using HLAAssure SE sequence-based typing kit (TBG Biotechnology Corp., Taiwan). The genotypes were determined by using the International ImMunoGeneTics database (<https://www.ebi.ac.uk/ipd/imgt/hla/>) [22]. At least two-field resolution of HLA-DRB1 alleles was identified. In this study, a two-field resolution was used for the analysis.

2.3 | Statistical Analysis

Allele frequencies and the Hardy–Weinberg equilibrium (HWE) were determined using PyPop 0.7.0 [23]. Differences in allele frequencies between patients and controls were assessed using the Chi-square test with Yates correction or Fisher's exact test where appropriate (one expected number < 5). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each comparison [24]. The Bonferroni correction was applied for multiple comparisons, $P_c = 1 - (1 - P)^n$, where P_c is the corrected p -value, P is the uncorrected value and n is the number of comparisons. After verifying family relationships, allele transmission with KD or CALs was tested using TDT by assessing the deviation from 50% of the transmission from parents to affected children (comparing the

TABLE 1 | Demography of Kawasaki disease patients and control subjects.

	Kawasaki disease <i>N</i> = 795 (%)	Without CALs <i>N</i> = 570 (%)	With CALs <i>N</i> = 225 (%)	Controls <i>N</i> = 946 (%)
Male	476 (59.9)	317 (55.6)	159 (70.7)	489 (51.7)
Female	319 (40.1)	253 (44.4)	66 (29.3)	457 (48.4)
Age at diagnosis or enrollment (year)	1.9 $\pm$ 1.6	1.9 $\pm$ 1.6	1.7 $\pm$ 1.6	12.3 $\pm$ 10.2 (734 controls)

Abbreviation: CALs, coronary artery lesions.

alleles transmitted to affected individuals to those not transmitted) [25–27]. A *P* value of < 0.05 indicated statistical significance.

3 | Results

HLA-DRB1 loci were successfully genotyped in all study participants. *HLA-DRB1*15:01* was significantly associated with KD compared with controls (OR, 1.44, *P* = 0.03, Table 2). Upon stratification by CALs, the association remained significant in KD patients without CALs (OR = 1.46, *P* = 0.04, Table 2). Furthermore, *HLA-DRB1*14:01* was a risk factor for KD with CALs (OR = 2.47, *P* = 0.004, Table 2) whereas *HLA-DRB1*12:02* was a protective factor against CALs (OR = 0.49, *P* = 0.01, Table 2). However, *HLA-DRB1*14:01* and *12:02 were only marginally associated with CALs when comparing KD patients with CALs with those without CALs (Table S1). In males, *HLA-DRB1*15:01* was a significant risk factor for KD when comparing patients with controls (OR = 1.73, *P* = 0.01, Table 3) and when comparing KD patients without CALs with

controls (OR = 1.82, *P* = 0.009 Table 3). *HLA-DRB1*14:01* remained significantly associated with CALs (OR = 3.04, *P* = 0.006, Table 3), but not *HLA-DRB1*12:02*. The association between *HLA-DRB1*14:01* and CALs did not remain significant in male KD patients (Table S2). Furthermore, no alleles showed a significant association with KD or CALs in the female patients (Table S3). Additionally, there were no significant differences in allele frequencies between male and female patients (Table S4).

In the family-based study involving 180 trios, *HLA-DRB1*15:01* demonstrated significant overtransmission to KD patients (OR = 3.35; 95% CI, 2.20–5.78; *P* = 1.19E-06, Table 4). This overtransmission remained significant in KD patients without CALs (OR = 4.42; 95% CI, 2.59–10.08; *P* = 6.24E-06), in male KD patients (OR = 2.81; 95% CI, 1.68–5.58; *P* = 0.003), and in male KD patients without CALs (OR = 3.22; 95% CI, 1.69–8.84; *P* = 0.02, Table 4). In contrast, *HLA-DRB1*14:01* and *12:02 showed no significant deviation from the expected transmission (Table 4).

TABLE 2 | Distribution of HLA-DRB1 alleles in children with Kawasaki disease and controls.^a

DRB1 allele	KD <i>n</i> (%)	Without CALs <i>n</i> (%)	With CALs <i>n</i> (%)	Controls <i>n</i> (%)	KD vs. controls		Without CALs vs. controls		With CALs vs. controls	
					OR	<i>P</i>	OR	<i>P</i>	OR	<i>P</i>
03:01	113 (7.1)	81 (7.1)	32 (7.1)	159 (8.4)						
04:03	37 (2.3)	29 (2.5)	8 (1.8)	69 (3.6)						
04:04	11 (0.7)	9 (0.8)	2 (0.4)	19 (1.0)						
04:05	120 (7.5)	84 (7.4)	36 (8.0)	129 (6.8)						
04:06	47 (3.0)	33 (2.9)	14 (3.1)	46 (2.4)						
07:01	45 (2.8)	32 (2.8)	13 (2.9)	50 (2.6)						
08:03	153 (9.6)	115 (10.1)	38 (8.4)	156 (8.2)						
09:01	240 (15.1)	163 (14.3)	77 (17.1)	314 (16.6)						
11:01	100 (6.3)	70 (6.1)	30 (6.7)	142 (7.5)						
12:01	59 (3.7)	42 (3.7)	17 (3.8)	68 (3.6)						
12:02	137 (8.6)	112 (9.8)	25 (5.6)	203 (10.7)					0.49	0.01
13:02	54 (3.4)	35 (3.1)	19 (4.2)	47 (2.5)						
14:01	60 (3.8)	35 (3.1)	25 (5.6)	44 (2.3)					2.47	0.004
14:05	29 (1.8)	18 (1.6)	11 (2.4)	44 (2.3)						
14:54	19 (1.2)	19 (1.7)	0 (0.0)	22 (1.2)						
15:01	173 (10.9)	126 (11.1)	47 (10.4)	148 (7.8)	1.44	0.03	1.46	0.04		
15:02	39 (2.5)	26 (2.3)	13 (2.9)	39 (2.1)						
16:02	73 (4.6)	53 (4.6)	20 (4.4)	103 (5.4)						
Others ^b	81 (5.1)	62 (5.4)	23 (5.1)	90 (4.8)						
Total	1590 (100)	1140 (100)	450 (100)	1892 (100)						

Note: HWE: *p* = 0.17 in KD; *p* = 0.64 in KD without CALs; *p* = 0.67 in KD with CALs; *p* = 0.15 in controls. The correction number is 18 excluding others.

Abbreviations: KD, Kawasaki disease; OR, odds ratio; *P*, Bonferroni corrected *p*-value.

^aBold indicates statistical significance (*P* < 0.05).

^bOthers include *DRB1*01:01*, *02:02*, *04:01*, *04:02*, *04:07*, *04:10*, *05:01*, *08:02*, *08:09*, *10:01*, *11:04*, *11:06*, *13:01*, *13:12*, *13:19*, *14:02*, *14:03*, *14:04*, *14:07*, *14:18*, *14:43*, *14:101*, *15:04*, and *16:01*, each with a frequency of < 1% in both cases and controls across all comparisons, and therefore excluded from the statistical analysis.

TABLE 3 | Distribution of HLA-DRB1 alleles in male Kawasaki disease patients and male controls.^a

DRB1 allele	Male KD n (%)	Male KD without CALs n (%)	Male KD with CALs n (%)	Male controls n (%)	Male KD vs. Male Controls		Male KD without CLAs vs. Male Controls		Male KD with CALs vs. Male Controls	
					OR	Pc	OR	Pc	OR	Pc
03:01	69 (7.2)	46 (7.3)	23 (7.2)	92 (9.4)						
04:03	20 (2.1)	14 (2.2)	6 (1.9)	39 (4.0)						
04:05	68 (7.1)	46 (7.3)	22 (6.9)	61 (6.2)						
04:06	32 (3.4)	20 (3.2)	12 (3.8)	22 (2.2)						
07:01	21 (2.2)	15 (2.4)	6 (1.9)	27 (2.8)						
08:03	89 (9.3)	66 (10.4)	23 (7.2)	83 (8.5)						
09:01	141 (14.8)	87 (13.7)	54 (17.0)	174 (17.8)						
11:01	58 (6.1)	37 (5.8)	21 (6.6)	71 (7.3)						
12:01	40 (4.2)	25 (3.9)	15 (4.7)	37 (3.8)						
12:02	82 (8.6)	65 (10.3)	17 (5.3)	94 (9.6)						
13:02	32 (3.4)	19 (3.0)	13 (4.1)	25 (2.6)						
14:01	36 (3.8)	17 (2.7)	19 (6.0)	20 (2.0)					3.04	0.006
14:05	22 (2.3)	13 (2.1)	9 (2.8)	27 (2.8)						
14:54	9 (0.9)	9 (1.4)	0 (0.0)	13 (1.3)						
15:01	109 (11.4)	76 (12.0)	33 (10.4)	68 (7.0)	1.73	0.01	1.82	0.009		
15:02	27 (2.8)	17 (2.7)	10 (3.1)	22 (2.2)						
16:02	49 (5.1)	32 (5.0)	17 (5.3)	54 (5.5)						
Others ^b	48 (5.0)	30 (4.7)	18 (5.7)	49 (5.0)						
Total	952 (100)	634 (100)	318 (100)	978 (100)						

Note: HWE: $p=0.16$ in male KD; $p=0.12$ in male KD without CALs; $p=0.53$ in male KD with CALs; $p=0.25$ in controls. The correction number is 17 excluding others. Abbreviations: KD, Kawasaki disease; OR, odds ratio; Pc, Bonferroni corrected p -value.

^aBold indicates statistical significance ($Pc<0.05$).

^bOthers include DRB1*01:01, 04:01, 04:02, 04:04, 04:07, 04:10, 08:02, 08:09, 10:01, 11:04, 11:06, 13:01, 13:12, 14:03, 14:04, 14:07, 14:18, 15:04, and 16:01, each with a frequency of <1% in both cases and controls across all comparisons, and therefore excluded from the statistical analysis.

TABLE 4 | Transmission/disequilibrium test for DRB1 allele in families of children with KD.^a

Phenotype	DRB1 allele	Trio N	T no. (%)	U no.	OR (95% CI)	χ^2	p	Pc
KD	15:01	180	77 (77.0)	23	3.35 (2.20–5.78)	29.2	6.66E-08	1.19E-06
KD without CALs	15:01	116	53 (79.0)	12	4.42 (2.59–10.08)	25.9	3.67E-07	6.24E-06
KD with CALs	14:01	64	6 (75.0)	2				
KD with CALs	12:02	64	6 (28.0)	15				
KD (Male)	15:01	117	45 (73.0)	16	2.81 (1.68–5.58)	13.8	2.05E-04	0.003
KD without CALs (male)	15:01	69	29 (76.0)	9	3.22 (1.69–8.84)	10.5	1.18E-03	0.02
KD with CALs (male)	14:01	48	5 (71.0)	2				
KD with CALs (male)	12:02	48	4 (33.3)	8				

Note: The correction number is 18 in KD, with and without CALs, male with and without CALs; 17 in KD (male), KD without CALs (male).

Abbreviations: CALs, coronary artery lesions; CI, confidence interval; KD, Kawasaki disease; OR, odds ratio; Pc, Bonferroni corrected p -value; T, transmitted; U, untransmitted.

^aBold indicates statistical significance ($Pc<0.05$).

4 | Discussion

Our study identified a genetic linkage between the HLA-DRB1 locus and susceptibility to KD with *DRB1*15:01* showing significant association in all KD patients, in male patients, and in male patients without CALs. *HLA-DRB1*14:01* was also significantly associated with CALs in all patients and in male patients. In contrast, *HLA-DRB1*12:02* was significantly protective against CALs in KD patients; however, this protective effect was not observed after stratification by sex.

HLA-DR is one of the HLA class II gene loci, along with HLA-DP and HLA-DQ. It encodes a DR molecule composed of two polypeptide chains, α and β , forming a heterodimer. The α chain (DR α) is encoded by HLA-DRA, whereas the β chain (DR β) is encoded by HLA-DRB1 or other HLA-DRB genes within the HLA-DR locus [28]. Class II antigens, including DR molecules, are normally expressed on macrophages, dendritic cells, reticuloendothelial cells, and B cells [29]. These molecules present fragments of foreign antigens to CD4⁺ helper T cells, thereby regulating the adaptive immune response [30]. As of October 2025, 127 HLA-DRA alleles and 3892 HLA-DRB1 alleles have been identified [31]. Because HLA-DRB1, HLA-DQA1, and HLA-DQB1 are in strong linkage disequilibrium (LD) and form a tight haplotype, it is difficult to disentangle the individual contribution of each locus to disease association.

*HLA-DRB1*15:01* has also been reported to be associated with multiple sclerosis [32], systemic lupus erythematosus [33], narcolepsy [34], anti-glomerular basement membrane disease [35] and leprosy [36]. *DRB1*15:01* typically tags the extended haplotype *DRB1*15:01~DQA1*01:02~DQB1*06:02*. Due to tight LD, locus-specific effects cannot be distinguished without multi-locus genotyping; notably, in African Americans where LD is weaker, *DQB1*06:02*—rather than *DRB1*15:01*—shows the primary association with narcolepsy when conditioned appropriately [34]. We have not genotyped DQA1 and DQB1 and therefore could not assess LD with DQA1 or DQB1 or perform conditional analyses.

In a case-control study, a small sample size may lead to false-negative results due to insufficient statistical power or the need for correction for multiple comparisons—an issue particularly relevant when studying HLA loci, where numerous alleles are present at a single locus [37]. A previous study failed to detect an association between HLA-DRB1 and KD after applying corrections for multiple comparisons, likely due to inadequate sample size [19]. In contrast, we enrolled a substantially larger cohort of patients and controls, performed high-resolution typing of DRB1 alleles at the two-field level (Table S5). These measures enhanced our power to detect the alleles associated with KD. Case-control studies are susceptible to population stratification, which may lead to false-positive or false-negative associations [11]. Therefore, replication in an independent population or validation through a family-based study is required to confirm the findings.

The TDT evaluates whether, in case–parent trios, heterozygous parents transmit a specific marker allele to affected offspring more frequently than the Mendelian 50% expectation—providing

evidence of linkage in the presence of association [38]. As a family-based study design, the TDT is a robust method for detecting linkage between a genetic marker and a disease gene when association exists [35]. A significant overtransmission observed by TDT with singletons not only confirms the association but also indicates linkage between the marker and the disease locus [36]. It is not susceptible to population stratification. We applied the TDT to the trios to verify the association between *HLA-DRB1*15:01* and KD and to detect the linkage between HLA-DRB1 and KD susceptibility genes. Limitations of TDT are that association must be present, both parents' genotypes are typically required, and late-onset diseases may lack available parents.

The aetiology of KD remains unclear. Although IVIG, aspirin and steroids effectively manage KD, vascular complications persist. HLA is involved in the innate and adaptive immune responses [39]. Class II HLA-DR, -DQ, and -DP are important in defence against infections. HLA-DRB1 is associated with many human mucocutaneous diseases, such as Stevens–Johnson syndrome/toxic epidermal necrolysis and drug-induced liver injury [40–43]. *HLA-DRB1*15:01* confers risk to multiple sclerosis through *DRB1*15:01*-dependent and DNA methylation-mediated levels of expression [44]. The differentially methylated region of *HLA-DRB1*15:01* may affect epitope expression in autoimmune diseases; thereby, it may contribute to the pathogenesis of KD [44]. In the acute stage of KD, immune factors, such as T cells, cytokines and adhesion molecules, are activated and contribute to the KD pathogenesis with delayed leukocyte apoptosis [45]. Additionally, macrophage activation alters T helper and regulatory cell functions and leads to the dysregulation of immune response in patients with KD [46, 47].

5 | Limitations

The HLA complex is the most gene-dense region of the human genome, yet our analysis was limited to the HLA-DRB1 locus [48]. Other loci within the HLA class II region, including HLA-DQA1, -DQB1, and -DPB1, as well as class I loci and T- and B-cell receptor genes warrant further investigation. Additionally, our study was conducted exclusively in a Taiwanese population; thus the findings should be validated in other ethnic groups to confirm their generalisability.

6 | Conclusions

Our study identified significant associations between *HLA-DRB1*15:01*, **14:01*, and **12:02* and KD. The association between *HLA-DRB1*15:01* and KD was further verified by TDT, indicating a genetic linkage between the HLA-DRB1 locus and KD susceptibility.

Author Contributions

Hsin Chi, Horng-Woei Yang, Yann-Jinn Lee and Nan-Chang Chiu conceived and conducted the experiments and analysed the data. Hsin Chi and Horng-Woei Yang wrote the manuscript draft. Nan-Chang Chiu and Yann-Jinn Lee edited the manuscript. Fu-Yuan Huang,

Ming-Ren Chen, Lung Chang, Daniel Tsung-Ning Huang, Ching-Ying Huang and Hsin Chi recruited KD patients and their families for the study. Ming-Ren Chen performed echocardiography on patients. Yann-Jinn Lee and Kuang-Chun Hu recruited the controls and participated in the discussion. All authors have read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. T. Kawasaki, "Acute Febrile Mucocutaneous Syndrome With Lymphoid Involvement With Specific Desquamation of the Fingers and Toes in Children," *Arerugi* 16, no. 3 (1967): 178–222.
2. T. Kawasaki, F. Kosaki, S. Okawa, I. Shigematsu, and H. Yanagawa, "A New Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome (MLNS) Prevailing in Japan," *Pediatrics* 54, no. 3 (1974): 271–276.
3. C. R. Kang, J. S. Lee, and Y. J. Choe, "Global Incidence of Kawasaki Disease: A Systematic Review," *Cardiology in the Young* 35, no. 5 (2025): 1028–1039.
4. B. W. McCrindle, A. H. Rowley, J. W. Newburger, et al., "Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association," *Circulation* 135, no. 17 (2017): e927–e999.
5. J. W. Newburger, M. Takahashi, J. C. Burns, et al., "The Treatment of Kawasaki Syndrome With Intravenous Gamma Globulin," *New England Journal of Medicine* 315, no. 6 (1986): 341–347.
6. K. A. Taubert, A. H. Rowley, and S. T. Shulman, "Seven-Year National Survey of Kawasaki Disease and Acute Rheumatic Fever," *Pediatric Infectious Disease Journal* 13, no. 8 (1994): 704–708.
7. M. A. Gonzalez-Gay, E. Heras-Recuero, T. Blazquez-Sanchez, et al., "Genetics of Vasculitis," *Best Practice & Research. Clinical Rheumatology* 4 (2024): 101969.
8. S. Kato, M. Kimura, K. Tsuji, et al., "HLA Antigens in Kawasaki Disease," *Pediatrics* 61, no. 2 (1978): 252–255.
9. Y. Onouchi, "Molecular Genetics of Kawasaki Disease," *Pediatric Research* 65, no. 5 Pt 2 (2009): 46R–54R.
10. A. M. Krensky, W. Berenberg, K. Shanley, and E. J. Yunis, "HLA Antigens in Mucocutaneous Lymph Node Syndrome in New England," *Pediatrics* 67, no. 5 (1981): 741–743.
11. G. Keren, Y. L. Danon, S. Orgad, R. Kalt, and E. Gazit, "HLA Bw51 Is Increased in Mucocutaneous Lymph Node Syndrome in Israeli Patients," *Tissue Antigens* 20, no. 2 (1982): 144–146.

12. J. H. Oh, J. W. Han, S. J. Lee, et al., "Polymorphisms of Human Leucocyte Antigen Genes in Korean Children With Kawasaki Disease," *Pediatric Cardiology* 29, no. 2 (2008): 402–408.
13. M. R. Chen, T. Y. Chang, N. C. Chiu, et al., "Validation of Genome-Wide Associated Variants for Kawasaki Disease in a Taiwanese Case-Control Sample," *Scientific Reports* 10, no. 1 (2020): 11756.
14. Y. Huang, Y. J. Lee, M. R. Chen, et al., "Polymorphism of Transmembrane Region of MICA Gene and Kawasaki Disease," *Experimental and Clinical Immunogenetics* 17, no. 3 (2000): 130–137.
15. Q. Ye, F. Q. Gong, S. Q. Shang, and J. Hu, "Intravenous Immunoglobulin Treatment Responsiveness Depends on the Degree of CD8+ T Cell Activation in Kawasaki Disease," *Clinical Immunology* 171 (2016): 25–31.
16. N. Fildes, J. C. Burns, J. W. Newburger, W. Klitz, and A. B. Begovich, "The HLA Class II Region and Susceptibility to Kawasaki Disease," *Tissue Antigens* 39, no. 2 (1992): 99–101.
17. C. C. Chang, B. R. Hawkins, H. K. Kao, C. B. Chow, and Y. L. Lau, "Human Leucocyte Antigens in Southern Chinese With Kawasaki Disease," *European Journal of Pediatrics* 151, no. 11 (1992): 866.
18. K. S. Barron, E. D. Silverman, J. C. Gonzales, M. St Clair, K. Anderson, and J. D. Reveille, "Major Histocompatibility Complex Class II Alleles in Kawasaki Syndrome—Lack of Consistent Correlation With Disease or Cardiac Involvement," *Journal of Rheumatology* 19, no. 11 (1992): 1790–1793.
19. F. Y. Huang, T. Y. Chang, M. R. Chen, et al., "Genetic Variations of HLA-DRB1 and Susceptibility to Kawasaki Disease in Taiwanese Children," *Human Immunology* 68, no. 1 (2007): 69–74.
20. S. Shrestha, H. W. Wiener, B. Aissani, A. Shendre, J. Tang, and M. A. Portman, "Imputation of Class I and II HLA Loci Using High-Density SNPs From ImmunoChip and Their Associations With Kawasaki Disease in Family-Based Study," *International Journal of Immunogenetics* 42, no. 3 (2015): 140–146.
21. Y. J. Lee, C. Y. Huang, W. H. Ting, et al., "Association of an IL-4 Gene Haplotype With Graves Disease in Children: Experimental Study and Meta-Analysis," *Human Immunology* 72, no. 3 (2011): 256–261.
22. J. Robinson, J. A. Halliwell, J. D. Hayhurst, P. Flicek, P. Parham, and S. G. E. Marsh, "The IPD and IMGT/HLA Database: Allele Variant Databases," *Nucleic Acids Research* 43, no. Database issue (2015): D423–D431.
23. A. K. Lancaster, R. M. Single, O. D. Solberg, M. P. Nelson, and G. Thomson, "PyPop Update—A Software Pipeline for Large-Scale Multilocus Population Genomics," *Tissue Antigens* 69, no. Suppl 1 (2007): 192–197.
24. Y. J. Lee, M. R. Chen, W. C. Chang, F. S. Lo, and F. Y. Huang, "A Freely Available Statistical Program for Testing Associations," *MD Computing* 15, no. 5 (1998): 327–330.
25. R. S. Spielman, R. E. McGinnis, and W. J. Ewens, "Transmission Test for Linkage Disequilibrium: The Insulin Gene Region and Insulin-Dependent Diabetes Mellitus (IDDM)," *American Journal of Human Genetics* 52, no. 3 (1993): 506–516.
26. D. J. Schaid, "Transmission Disequilibrium, Family Controls, and Great Expectations," *American Journal of Human Genetics* 63, no. 4 (1998): 935–941.
27. E. Kawasaki, J. Noble, H. Erlich, C. L. Mulgrew, P. R. Fain, and G. S. Eisenbarth, "Transmission of DQ Haplotypes to Patients With Type 1 Diabetes," *Diabetes* 47, no. 12 (1998): 1971–1973.
28. M. van Lith, R. M. McEwen-Smith, and A. M. Benham, "HLA-DP, HLA-DQ, and HLA-DR Have Different Requirements for Invariant Chain and HLA-DM," *Journal of Biological Chemistry* 285, no. 52 (2010): 40800–40808.
29. D. Turner, "The Human Leucocyte Antigen (HLA) System," *Vox Sanguinis* 87, no. Suppl 1 (2004): 87–90.

30. P. A. Roche and K. Furuta, "The Ins and Outs of MHC Class II-Mediated Antigen Processing and Presentation," *Nature Reviews. Immunology* 15, no. 4 (2015): 203–216.
31. J. Robinson, D. J. Barker, X. Georgiou, M. A. Cooper, P. Flicek, and S. G. E. Marsh, "IPD-IMGT/HLA Database," *Nucleic Acids Research* 48, no. D1 (2020): D948–D955.
32. J. A. Hollenbach and J. R. Oksenberg, "The Immunogenetics of Multiple Sclerosis: A Comprehensive Review," *Journal of Autoimmunity* 64 (2015): 13–25.
33. H. Schmidt, D. Williamson, and A. Ashley-Koch, "HLA-DR15 Haplotype and Multiple Sclerosis: A HuGE Review," *American Journal of Epidemiology* 165, no. 10 (2007): 1097–1109.
34. T. Miyagawa and K. Tokunaga, "Genetics of Narcolepsy," *Human Genome Variation* 6 (2019): 4.
35. M. Segelmark and T. Hellmark, "Anti-Glomerular Basement Membrane Disease: An Update on Subgroups, Pathogenesis and Therapies," *Nephrology, Dialysis, Transplantation* 34, no. 11 (2019): 1826–1832.
36. M. Dallmann-Sauer, V. M. Fava, C. Gzara, et al., "The Complex Pattern of Genetic Associations of Leprosy With HLA Class I and Class II Alleles Can Be Reduced to Four Amino Acid Positions," *PLoS Pathogens* 16, no. 8 (2020): e1008818.
37. Wellcome Trust Case Control C, "Genome-Wide Association Study of 14,000 Cases of Seven Common Diseases and 3,000 Shared Controls," *Nature* 447, no. 7145 (2007): 661–678.
38. H. Ackerman, S. Usen, M. Jallow, F. Sisay-Joof, M. Pinder, and D. P. Kwiatkowski, "A Comparison of Case-Control and Family-Based Association Methods: The Example of Sickle-Cell and Malaria," *Annals of Human Genetics* 69, no. Pt 5 (2005): 559–565.
39. J. A. Boquett, J. Sauter, A. H. Schmidt, M. Maiers, and J. A. Hollenbach, "Human Leukocyte Antigen Variation Is Associated With Cytomegalovirus Serostatus in Healthy Individuals," *American Journal of Human Genetics* 112 (2025): 913–926.
40. J. C. Roujeau, J. P. Kelly, L. Naldi, et al., "Medication Use and the Risk of Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis," *New England Journal of Medicine* 333, no. 24 (1995): 1600–1607.
41. R. A. Schwartz, P. H. McDonough, and B. W. Lee, "Toxic Epidermal Necrolysis: Part I. Introduction, History, Classification, Clinical Features, Systemic Manifestations, Etiology, and Immunopathogenesis," *Journal of the American Academy of Dermatology* 69, no. 2 (2013): 173.e1–173.e13.
42. C. Ferrandiz-Pulido and V. Garcia-Patos, "A Review of Causes of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Children," *Archives of Disease in Childhood* 98, no. 12 (2013): 998–1003.
43. H. Y. Lee, S. A. Walsh, and D. Creamer, "Long-Term Complications of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN): The Spectrum of Chronic Problems in Patients Who Survive an Episode of SJS/TEN Necessitates Multidisciplinary Follow-Up," *British Journal of Dermatology* 177, no. 4 (2017): 924–935.
44. L. Kular, Y. Liu, S. Ruhrmann, et al., "DNA Methylation as a Mediator of *HLA-DRB1*15:01* and a Protective Variant in Multiple Sclerosis," *Nature Communications* 9, no. 1 (2018): 2397.
45. M. R. Chen, H. C. Kuo, Y. J. Lee, et al., "Phenotype, Susceptibility, Autoimmunity, and Immunotherapy Between Kawasaki Disease and Coronavirus Disease-19 Associated Multisystem Inflammatory Syndrome in Children," *Frontiers in Immunology* 12 (2021): 632890.
46. A. Muise, S. E. Tallett, and E. D. Silverman, "Are Children With Kawasaki Disease and Prolonged Fever at Risk for Macrophage Activation Syndrome?," *Pediatrics* 112, no. 6 Pt 1 (2003): e495.
47. K. Furuno, T. Yuge, K. Kusuhara, et al., "CD25+CD4+ Regulatory T Cells in Patients With Kawasaki Disease," *Journal of Pediatrics* 145, no. 3 (2004): 385–390.
48. D. Meyer, C. A. Vr, B. D. Bitarello, C. B. Dy, and K. Nunes, "A Genomic Perspective on HLA Evolution," *Immunogenetics* 70, no. 1 (2018): 5–27.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Distribution of HLA-DRB1 alleles in Kawasaki disease patients with and without CALs. **Table S2:** Distribution of HLA-DRB1 alleles in male Kawasaki disease patients with and without CALs. **Table S3:** Distribution of HLA-DRB1 alleles in female Kawasaki disease patients and female controls. **Table S4:** Distribution of HLA-DRB1 alleles in male and female Kawasaki disease patients. **Table S5:** Population comparison of the HLA-DRB1 allele group frequencies with those of 2007.