

Letter to the Editor

Anti-IFN- γ autoantibodies are strongly associated with HLA-DRB1*15:02/16:02 and HLA-DQB1*05:01/05:02 across Southeast Asia

To the Editor:

Neutralizing anti-IFN- γ autoantibodies (nAIGAs) are a recently recognized mechanism of infection with disseminated nontuberculous mycobacteria and other intracellular opportunists, with the phenotype being similar to genetic disruption of IFN- γ immunity.¹⁻³ In the last decade, there has been a high prevalence of nAIGAs, nearly completely restricted to patients from Southeast Asia, mostly from Thailand and Taiwan,^{4,5} with a few from Hong Kong, Japan, and Western countries but originally from Southeast Asia.⁶ This narrow ethnic and geographic distribution of nAIGA-associated immunodeficiency suggests a critical interplay between unique genetic and environmental factor(s). HLAs are among the strongest and reproducible genetic factors associated with autoimmune diseases.⁷ In a previous work, we documented a strong association between HLA class II alleles, HLA-DRB1*16:02 and HLA-DQB1*05:02, and nAIGAs in 17 patients from Taiwan, providing the first evidence of genetic factors involved in this disease.⁴ The haplotype DRB1*16:02-DQB1*05:02 is common in Asian populations (2.6% to 18.8%) and could explain the much higher prevalence of nAIGAs in patients from Taiwan and other Asian countries.⁸

Here, we investigated the association of HLA-DQB1 and HLA-DRB1 alleles in patients with nAIGAs from Taiwan and other Asian countries. The clinical characteristics of subjects and details about methods are available in this article's Online Repository at www.jacionline.org. This association was also established through comparison of 78 Thai patients and 101 controls, with an odds ratio (OR) of 3.80 (95% CI, 2.14-6.77; $P_{\text{FDR}} = 1 \times 10^{-4}$) for DRB1*16:02 and 2.56 (95% CI, 1.62-4.07; $P_{\text{FDR}} = 5 \times 10^{-4}$) for DQB1*05:02 (Table I; see Tables E1 and E2 in this article's Online Repository at www.jacionline.org). We also identified 2 new strongly associated alleles in Thai patients, HLA-DRB1*15:02 and HLA-DQB1*05:01, with an OR of 5.33 (95% CI, 3.15-9.01; $P_{\text{FDR}} = 1.02 \times 10^{-8}$) and 4.19 (95% CI, 2.39-7.34; $P_{\text{FDR}} = 9.61 \times 10^{-6}$), respectively (Table I). Identification of 2 risk alleles in the DRB1 locus and 2 risk alleles in the DQB1 locus might be explained by haplotypes in high linkage disequilibrium in DRB1*16:02-DQB1*05:02 and DRB1*15:02-DQB1*05:01 ($D' = 1$, $r^2 = 0.72$ and $D' = 0.92$, $r^2 = 0.79$, respectively).

Seeking to confirm the association identified between HLA class II alleles and nAIGAs in 17 Taiwanese patients,⁴ we enrolled 27 additional Taiwanese patients into our cohort. Again, we found that DRB1*16:02 and DQB1*05:02 were the most frequently observed alleles (43.18% and 47.73%, respectively) in Taiwanese patients (OR = 8.36 with $P_{\text{FDR}} = 4.53 \times 10^{-9}$ for DRB1*16:02 and OR = 6.54 with $P_{\text{FDR}} = 1.05 \times 10^{-8}$) (Table I; see Tables E3 and E4 in this article's Online Repository at www.jacionline.org). Interestingly, in this larger Taiwanese cohort, DRB1*15:02 was significantly associated with nAIGAs (OR = 14.42; $P_{\text{FDR}} = .0084$). Another risk allele DQB1*05:01 in the Thai cohort was only mildly associated with the presence

of nAIGAs and not significant after false-discovery rate corrections. Therefore, our results confirmed our previous finding of DRB1*16:02 and DQB1*05:02 association and showed that DRB1*15:02 was associated with nAIGAs not only in Thai patients but also in Taiwanese patients.

Interestingly, we observed each of the 4 aforementioned risk alleles to demonstrate disproportionately high rates of coexpression in patients compared with controls as well. All 78 Thai patients (100%) carried at least 1 allele of DRB1*15:02 or 16:02 versus 38.6% in controls (Table II). Furthermore, 12 patients (15.4%) and 1 control (1.0%) carried both DRB1*15:02 and 16:02. Similarly, in the DQB1 locus, 76 of 78 (97.4%) patients and 50 of 101 (49.5%) controls carried at least 1 allele of DQB1*05:01 or 05:02 (OR = 38.76; 95% CI, 9.03-166.43; $P = 8.69 \times 10^{-7}$). Nineteen of 78 (24.4%) patients and 4 of 101 (4.0%) controls carried DQB1*05:01 or 05:02 in both alleles (OR = 121.12; 95% CI, 20.48-716.26; $P = 1.22 \times 10^{-7}$) (Table II). These results implicate a synergistic effect for both DRB1*15:02 and 16:02, as well as DQB1*05:01 and 05:02 alleles for the risk of nAIGA production.

Beyond Thailand and Taiwan, patients with nAIGA-associated immunodeficiency have been reported across East Asia, including Hong Kong, the Philippines, Vietnam, Laos, and Japan. We were interested in knowing whether the risk alleles were present among them. We analyzed the HLA class II loci in 8 Han Chinese patients from Hong Kong, all of whom carried DRB1*15:02 (2 alleles) or DRB1*16:02 (9 alleles) for the DRB1 locus and DQB1*05:02 (11 alleles) for the DQB1 locus (see Table E5 in this article's Online Repository at www.jacionline.org). These findings further support DRB1*16:02 and DQB1*05:02 as risk alleles in those of Han ethnicity, regardless of country of origin. We then analyzed the HLA class II locus in patients from the Philippines (7), Vietnam (4), and Laos (3). Again, DRB1*15:02 and DRB1*16:02 were the most frequent alleles found in DRB1 locus (60.7% and 14.3%, respectively). DQB1*05:01 and DQB1*05:02 were also found with a high frequency at the DQB1 locus (14.3% and 64.3%, respectively). All 7 Filipino patients carried DRB1*15:02 allele. Only 1 of the 4 Vietnamese patients did not carry the risk alleles. In addition, we noted that many of them had risk alleles on both loci. The American white patient with nAIGAs did not carry any of the identified risk alleles, underscoring that disease pathogenesis is likely complex.

Because of strong linkage disequilibrium, it is difficult to determine which locus has the greatest ability to induce nAIGAs. However, the fact that DRB1*15:02 and DRB1*16:02 are more frequently found in Thailand and Taiwan suggests that the pathogenic capacity of these loci may surpass that of DQB1*05:01 and DQB1*05:02. DRB1*15:02 and DRB1*16:02 are commonly found in Southeast Asians, Americans, and Pacific Islanders, but rarely found in whites and Africans (see Fig E1 in this article's Online Repository at www.jacionline.org),⁹ whereas DQB1*05:01 and DQB1*05:02 are commonly found in other populations. Moreover, the ORs of DRB1*16:02 and DRB1*15:02 were higher than those of DQB1*05:02 and DQB1*05:01 in 2 studied cohorts, again supporting the hypothesis that DRB1 loci more robustly contribute to nAIGA pathogenesis. Interestingly, DRB1*15:02 and DQB1*05:02 and other risk alleles are also commonly found in

TABLE I. The association of HLA-DRB1 and -DQB1 alleles with anti-IFN- γ autoantibodies in Thailand and Taiwan

Allele type	Control		Patient		χ^2	P_{χ^2}	Fisher exact P value	OR (95% CI)	P_{logistic}	P_{FDR}
	Count*	%†	Count*	%†						
Thailand	N = 101		N = 78							
DRB1*15:02	25	12.38	67	42.95	43.0875	5.23×10^{-11}	8.26×10^{-11}	5.33 (3.15-9.01)	4.26×10^{-10}	1.02×10^{-8}
DRB1*16:02	20	9.90	46	29.49	22.4560	2.15×10^{-6}	3.81×10^{-6}	3.80 (2.14-6.77)	5.41×10^{-6}	.0001
DQB1*05:01	21	10.40	51	32.69	27.2348	1.80×10^{-7}	2.57×10^{-7}	4.19 (2.39-7.34)	6.00×10^{-7}	9.61×10^{-6}
DQB1*05:02	44	21.78	65	41.67	16.4347	.0001	.0001	2.56 (1.62-4.07)	.0001	.0005
Taiwan	N = 102		N = 44							
DRB1*15:02	2	0.98	11	12.50	19.1789	1.19×10^{-5}	.0001	14.42 (3.13-66.53)	.0006	.0084
DRB1*16:02	17	8.33	38	43.18	48.8374	2.78×10^{-12}	2.53×10^{-11}	8.36 (4.36-16.04)	1.68×10^{-10}	4.53×10^{-9}
DQB1*05:01	7	3.43	10	11.36	7.0552	.0079	.0127	3.61 (1.33-9.82)	.0120	.1008
DQB1*05:02	25	12.25	42	47.73	43.7541	3.72×10^{-11}	2.21×10^{-10}	6.54 (3.62-11.81)	4.99×10^{-10}	1.05×10^{-8}

*Number of alleles observed.

†Allele frequencies found in cohort.

TABLE II. The synergistic effect and association of 2 codominant haplotypes DRB1*16:02/DQB1*05:02 and DRB1*15:02/DQB1*05:01 with anti-IFN- γ autoantibodies in Thai patients

Allele type	Status	Control (N = 101)		Patient (N = 78)		Logistic regression 1*		Logistic regression 2†	
		Count‡	%§	Count‡	%§	OR (95% CI)	P value	OR (95% CI)	P value
DRB1*15:02	Carrying both	4	4.0	17	21.8	6.68 (2.17-21.03)	9.71×10^{-4}	12.14 (3.76-39.17)	2.94×10^{-5}
	Carrying 1	17	16.8	33	42.3	3.62 (1.82-7.21)	2.45×10^{-4}	5.55 (2.68-11.47)	3.79×10^{-6}
	None	80	79.2	28	35.9	0.15 (0.08-0.29)	1.77×10^{-8}	Reference	
DRB1*16:02	Carrying both	1	1.0	6	7.7	8.33 (0.98-70.73)	.0520	12.94 (1.51-111.26)	.0200
	Carrying 1	18	17.8	34	43.6	3.56 (1.81-7.02)	2.41×10^{-4}	4.08 (2.05-8.12)	6.37×10^{-5}
	None	82	81.2	38	48.7	0.22 (0.11-0.43)	8.96×10^{-6}	Reference	
DQB1*05:01	Carrying both	2	2.0	8	10.3	5.66 (1.17-27.45)	.0315	9.37 (1.89-46.38)	.0061
	Carrying 1	17	16.8	35	44.9	4.02 (2.03-7.99)	7.03×10^{-5}	4.82 (2.39-9.73)	1.11×10^{-5}
	None	82	81.2	35	44.9	0.19 (0.10-0.37)	1.04×10^{-6}	Reference	
DQB1*05:02	Carrying both	9	8.9	13	16.7	2.04 (0.83-5.07)	.1224	3.67 (1.4-9.61)	.0082
	Carrying 1	26	25.7	39	50.0	2.89 (1.54-5.41)	9.68×10^{-4}	3.81 (1.94-7.46)	9.74×10^{-5}
	None	66	65.4	26	33.3	0.27 (0.14-0.5)	3.07×10^{-5}	Reference	
DRB1*15:02/16:02	Carrying both	1	1.0	—	15.4	18.18 (2.31-143.14)	.0059	NA	NA
	Carrying either one	38	37.6	66	84.6	9.12 (4.37-19.02)	3.80×10^{-9}	NA	NA
	None	62	61.4	0	0	NA	NA	Reference	
DQB1*05:01/05:02	Carrying at least 1	39	38.6	78	100.0	NA	NA	—	—
	Carrying both	4	4.0	19	24.4	7.81 (2.53-24.07)	3.46×10^{-4}	121.12 (20.48-716.26)	1.22×10^{-7}
	Carrying either one	46	45.5	57	73.1	3.25 (1.72-6.13)	2.82×10^{-4}	31.60 (7.3-136.77)	3.86×10^{-6}
	None	51	50.5	2	2.6	0.03 (0.01-0.11)	8.69×10^{-7}	Reference	
	Carrying at least 1	50	49.5	76	97.4	38.76 (9.03-166.43)	8.69×10^{-7}	—	—

NA, Nonapplicable.

*Logistic regression 1 was carried out comparing each status group versus else.

†Logistic regression 2 was carried out within the 3 status groups: "Carrying both," "Carrying either one," and "None" by setting the "None" group as reference to generate the ORs and P values.

‡Number of alleles observed.

§Allele frequencies found in cohort.

Malaysians, Cambodians, and Indonesians (Fig E1),⁹ although nAIGAs are yet to be identified in these regions. Based on the high frequency of at-risk alleles across East Asia, it is likely that nAIGAs are underrecognized in these regions.

In this study, we confirmed our previous findings that DRB1*16:02 and DQB1*05:02 are strongly associated with nAIGAs in Taiwanese patients and extended the observation to Thai patients with this syndrome. We also found new risk alleles DRB1*15:02 and DQB1*05:01, as the possibility that coexpression of risk alleles may further increase the risk of disease. Together, these findings suggest that these HLA class II alleles may confer a predisposition to nAIGA-associated immunodeficiency in Southeast Asia.

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METHODS

Patients and controls

Clinical information and diagnosis of nAIGAs of the patients reported here were previously described (C. L. Ku and C. Y. Chi, 2015, unpublished data).^{E1-E8} In brief, patients were unrelated and had mycobacterial infection and/or other opportunistic infections. High titer of nAIGAs was found in the plasma samples of patients by ELISA or other biochemical assays, and all subjects were free of HIV. Thai patients with (n = 78) and without (n = 101) anti-IFN- γ autoantibodies were enrolled from regions surrounding Bangkok or Khon Kaen. Three additional patients were included who were born in Thailand although they had emigrated before diagnosis^{E3} (J. L. Casanova, 2015, unpublished data). Taiwanese patients (n = 44) were enrolled from different regions across Taiwan, most or all of whom were self-identified as of Chinese/Han origin,^{E1,E2,E6} and were compared with Taiwanese controls (n = 102).^{E9} The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (103-2861C) and the National Institutes of Health (NCT00404560 and NCT00814827), and informed consent was obtained from the patients in accordance with the Declaration of Helsinki.

HLA typing for HLA-DRB1 and HLA-DQB1

Genomic DNA was prepared from patient and control whole blood samples using a phenol/chloroform extraction method. HLA genotypes were carried out by using SeCore DRB1 & DQB1 Locus Sequencing Kits (Invitrogen/Life Technologies, Brown Deer, Wis), and sequencing was run on an ABI 3730XL DNA analyzer (Applied Biosystems, Foster City, Calif) with uTYPE6.0 SBT software (Invitrogen) as described in the manufacturer's protocol.

Statistical analysis

To investigate the association of HLA-DRB1 and DQB1 alleles with anti-IFN- γ autoantibodies in the Taiwanese and Thai populations, the allele frequencies were compared between anti-IFN- γ autoantibody-positive patients and anti-IFN- γ autoantibody-negative controls using Pearson χ^2 test and Fisher exact test. The *P* values, ORs, and 95% CIs were also calculated using logistic regression models to assess the effect that each allele conferred. To account for multiple comparison problems, the *P* values corrected by Benjamini and Hochberg's false-discovery rate method were

calculated using the MULTTEST procedure in SAS 9.2 (SAS Institute, Cary, NC). An adjusted *P* value (*P*_{FDR}) of less than .05 indicated statistical significance. Pairwise linkage disequilibrium measures of the alleles within the same gene were analyzed using the ALLELE procedure in SAS/GENETICS. Three measures—the linkage disequilibrium coefficient, *D'*, and *r*²—were calculated.

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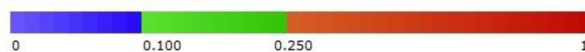
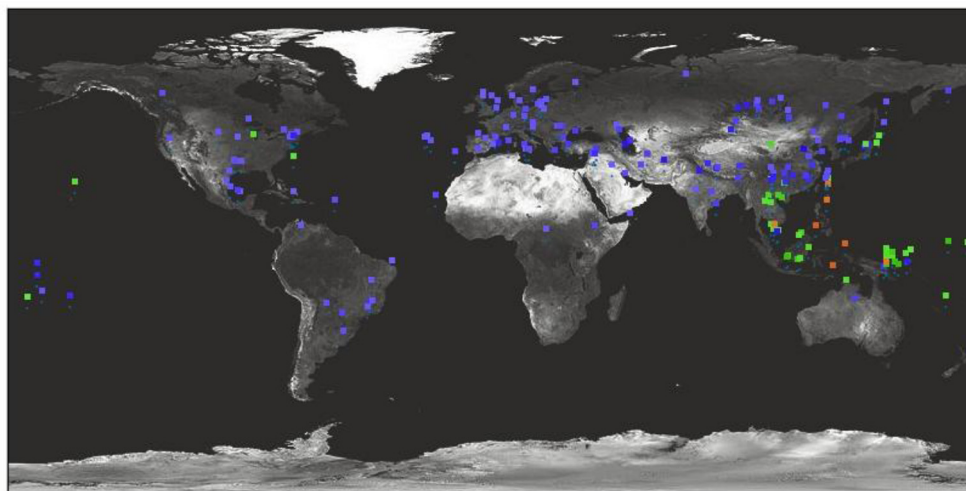
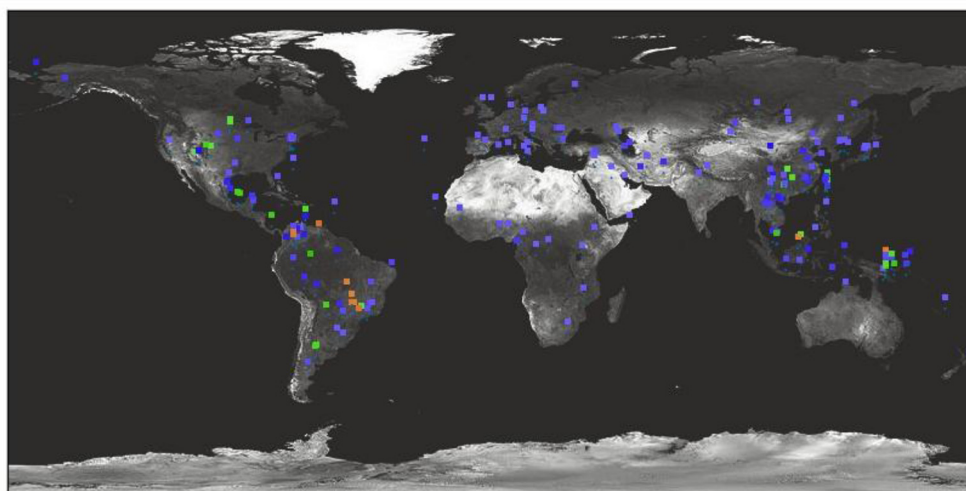
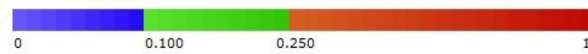
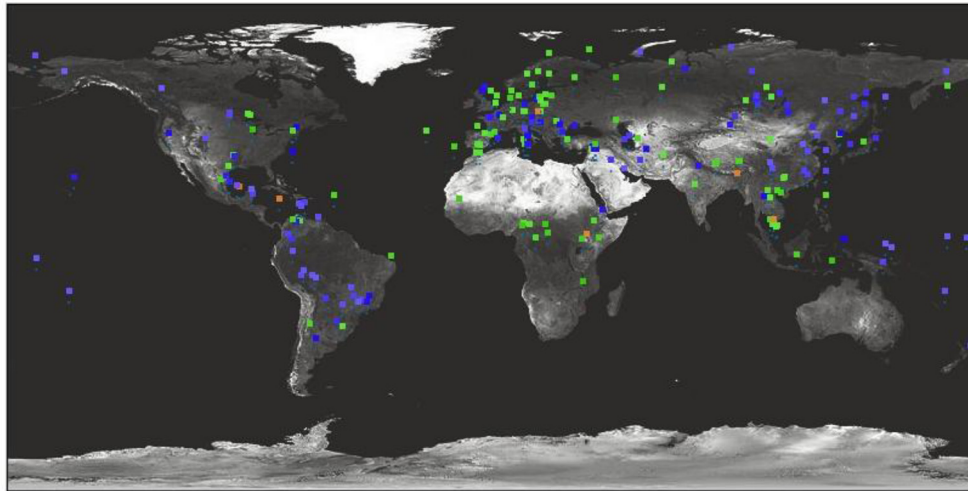
A**Allele: DRB1*15:02****B****Allele: DRB1*16:02**

FIG E1. Allele frequency variations of HLA-DRB1*15:02, HLA-DRB1*16:02, HLA-DQB1*05:01, and HLA-DRB1*05:02 across worldwide populations. The allele frequencies are presented with different colors, shown as the *color bar* below the figure. **A**, HLA-DRB1*15:02. **B**, HLA-DRB1*16:02. **C**, HLA-DQB1*05:01. **D**, HLA-DQB1*05:02. The data were screenshots from the New Allele Frequency Database (<http://www.allelefrequencies.net>).

C

Allele: DQB1*05:01

**D**

Allele: DQB1*05:02

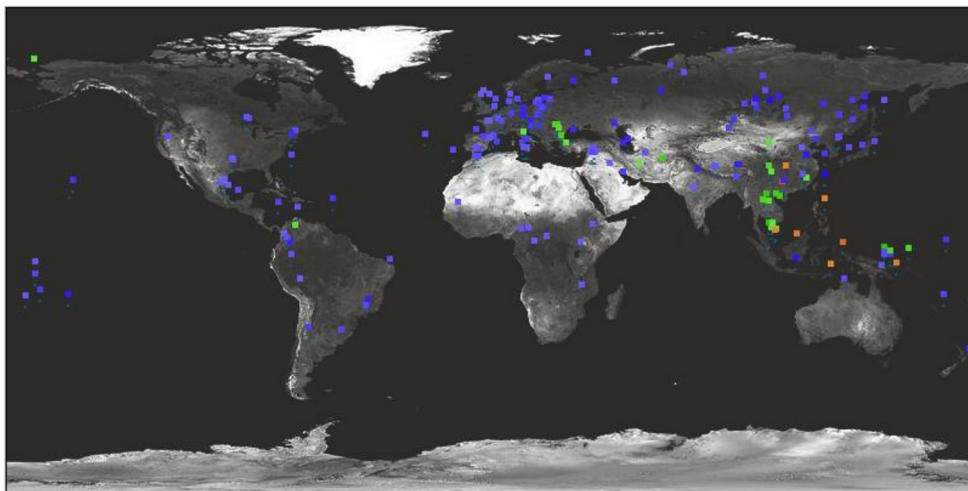
**FIG E1.** (Continued).

TABLE E1. The association of HLA-DRB1 alleles with anti-IFN- γ autoantibodies in Thailand

Allele type	Control (N = 101)		Patient (N = 78)				χ^2	P_{χ^2}	Fisher exact P value	OR (95% CI)	P_{logistic}	P_{FDR}
	Count*	%†	Count*	%†	Carrier‡	%§						
03:01	12	5.94	1	0.64	1	1.28	7.0644	.0079	.0084	0.10 (0.01-0.79)	.0293	.1170
04:03	1	0.50	0	0	0	0	0.7744	.3788	1.0000	NA	NA	NA
04:05	16	7.92	3	1.92	3	3.85	6.3005	.0121	.0156	0.23 (0.07-0.80)	.0206	.1170
04:06	4	1.98	0	0	0	0	3.1240	.0771	.1353	NA	NA	NA
05:27	0	0	1	0.64	1	1.28	1.2985	.2545	.4358	NA	NA	NA
07:01	12	5.94	6	3.85	6	7.69	0.8086	.3685	.4675	0.63 (0.23-1.73)	.3722	.9885
08:03	8	3.96	0	0	0	0	6.3194	.0119	.0108	NA	NA	NA
08:09	3	1.49	0	0	0	0	2.3364	.1264	.2603	NA	NA	NA
08:19	1	0.50	0	0	0	0	0.7744	.3788	1.0000	NA	NA	NA
09:01	21	10.40	6	3.85	6	7.69	5.4155	.0200	.0252	0.34 (0.14-0.88)	.0252	.1170
10:01	5	2.48	0	0	0	0	3.9161	.0478	.0711	NA	NA	NA
11:01	11	5.45	1	0.64	1	1.28	6.2719	.0123	.0150	0.11 (0.01-0.88)	.0371	.1272
11:06	1	0.50	1	0.64	1	1.28	0.0338	.8542	1.0000	1.30 (0.08-20.90)	.8546	.9885
12:01	1	0.50	0	0	0	0	0.7744	.3788	1.0000	NA	NA	NA
12:02	32	15.84	7	4.49	7	8.97	11.6905	.0006	.0005	0.25 (0.11-0.58)	.0013	.0105
13:02	1	0.50	2	1.28	2	2.56	0.6561	.4179	.5824	2.61 (0.23-29.05)	.4351	.9885
13:12	1	0.50	1	0.64	1	1.28	0.0338	.8542	1.0000	1.30 (0.08-20.90)	.8546	.9885
14:04	1	0.50	1	0.64	1	1.28	0.0338	.8542	1.0000	1.30 (0.08-20.90)	.8546	.9885
14:05	3	1.49	0	0	0	0	2.3364	.1264	.2603	NA	NA	NA
14:54	9	4.46	7	4.49	7	8.97	0.0002	.9885	1.0000	1.01 (0.37-2.77)	.9885	.9885
15:01	13	6.44	6	3.85	6	7.69	1.1744	.2785	.3456	0.58 (0.22-1.57)	.2837	.8510
15:02	25	12.38	67	42.95	50	64.10	43.0875	5.23×10^{-11}	8.26×10^{-11}	5.33 (3.15-9.01)	4.26×10^{-10}	1.02×10^{-8}
15:06	1	0.50	0	0	0	0	0.7744	.3788	1.0000	NA	NA	NA
16:02	20	9.90	46	29.49	40	51.28	22.4560	2.15×10^{-6}	3.81×10^{-6}	3.80 (2.14-6.77)	5.41×10^{-6}	.0001

NA, Nonapplicable.

*Number of alleles observed.

†Allele frequencies found in cohort.

‡Number of patients observed.

§Patients frequencies found in cohort.

TABLE E2. The association of HLA-DQB1 alleles with anti-IFN- γ autoantibodies in Thailand

Allele type	Control (N = 101)		Patient (N = 78)				χ^2	P_{χ^2}	Fisher exact <i>P</i> value	OR (95% CI)	P_{logistic}	P_{FDR}
	Count*	%†	Count*	%†	Carrier‡	%§						
02:01	12	5.94	2	1.28	2	2.56	5.0836	.0242	.0275	0.21 (0.05-0.93)	.0404	.1291
02:02	9	4.46	5	3.21	5	6.41	0.3662	.5451	.5951	0.71 (0.23-2.16)	.5469	.8750
03:01	38	18.81	8	5.13	8	10.26	14.7181	.0001	.0001	0.23 (0.11-0.52)	.0003	.0017
03:02	11	5.45	2	1.28	2	2.56	4.3603	.0368	.0456	0.23 (0.05-1.03)	.0551	.1468
03:03	23	11.39	7	4.49	7	8.97	5.4567	.0195	.0211	0.37 (0.15-0.88)	.0240	.0959
04:01	8	3.96	3	1.92	3	3.85	1.2267	.2680	.3606	0.48 (0.12-1.82)	.2786	.5573
04:02	5	2.48	0	0	0	0	3.9161	.0478	.0711	NA	NA	NA
05:01	21	10.40	51	32.69	43	55.13	27.2348	1.80×10^{-7}	2.57×10^{-7}	4.19 (2.39-7.34)	6.00×10^{-7}	9.61×10^{-6}
05:02	44	21.78	65	41.67	52	66.67	16.4347	.0001	.0001	2.56 (1.62-4.07)	.0001	.0005
05:03	5	2.48	0	0	0	0	3.9161	.0478	.0711	NA	NA	NA
05:18	0	0	2	1.28	2	2.56	2.6043	.1066	.1892	NA	NA	NA
06:01	19	9.41	7	4.49	7	8.97	3.1620	.0754	.0996	0.45 (0.19-1.11)	.0818	.1870
06:02	3	1.49	2	1.28	2	2.56	0.0264	.8710	1.0000	0.86 (0.14-5.22)	.8711	.9872
06:09	1	0.50	2	1.28	2	2.56	0.6561	.4179	.5824	2.61 (0.23-29.05)	.4351	.7736
07:01	1	0.50	0	0	0	0	0.7744	.3788	1.0000	NA	NA	NA
15:02	2	0.99	0	0	0	0	1.5532	.2127	.5069	NA	NA	NA

NA, Nonapplicable.

*Number of alleles observed.

†Allele frequencies found in cohort.

‡Number of patients observed.

§Patients frequencies found in cohort.

TABLE E3. The association of HLA-DRB1 alleles with anti-IFN- γ autoantibodies in Taiwan

Allele type	Control (N = 102)		Patient (N = 44)				χ^2	P_{χ^2}	Fisher exact <i>P</i> value	OR (95% CI)	P_{logistic}	P_{FDR}
	Count*	%†	Count*	%†	Carrier‡	%§						
01:01	1	0.49	0	0.00	0	0	0.4329	.5106	1.0000	NA	NA	NA
03:01	11	5.39	1	1.14	1	2.27	2.8256	.0928	.1155	0.20 (0.03-1.59)	.1282	.4944
04:03	10	4.90	0	0.00	0	0	4.4667	.0346	.0356	NA	NA	NA
04:04	3	1.47	1	1.14	1	2.27	0.0508	.8216	1.0000	0.77 (0.08-7.51)	.8221	.9923
04:05	14	6.86	11	12.50	9	20.45	2.4956	.1142	.1694	1.94 (0.84-4.46)	.1191	.4944
04:06	3	1.47	0	0.00	0	0	1.3076	.2528	.5563	NA	NA	NA
04:10	2	0.98	0	0.00	0	0	0.8687	.3513	1.0000	NA	NA	NA
07:01	2	0.98	1	1.14	1	2.27	0.0147	.9035	1.0000	1.16 (0.10-12.97)	.9036	.9923
08:03	24	11.76	1	1.14	1	2.27	8.8711	.0029	.0022	0.09 (0.01-0.65)	.0172	.1549
08:09	0	0.00	2	2.27	2	4.55	4.6683	.0307	.0901	NA	NA	NA
09:01	35	17.16	6	6.82	6	13.64	5.4446	.0196	.0263	0.35 (0.14-0.87)	.0243	.1640
10:01	4	1.96	0	0.00	0	0	1.7495	.1859	.3194	NA	NA	NA
11:01	12	5.88	3	3.41	3	6.82	0.7717	.3797	.5650	0.56 (0.16-2.05)	.3855	.9923
12:01	5	2.45	0	0.00	0	0	2.1944	.1385	.3270	NA	NA	NA
12:02	21	10.29	4	4.55	4	9.09	2.5952	.1072	.1173	0.41 (0.14-1.25)	.1171	.4944
13:01	1	0.49	0	0.00	0	0	0.4329	.5106	1.0000	NA	NA	NA
13:02	7	3.43	0	0.00	0	0	3.0938	.0786	.1065	NA	NA	NA
13:12	1	0.49	0	0.00	0	0	0.4329	.5106	1.0000	NA	NA	NA
14:03	1	0.49	0	0.00	0	0	0.4329	.5106	1.0000	NA	NA	NA
14:04	1	0.49	0	0.00	0	0	0.4329	.5106	1.0000	NA	NA	NA
14:05	2	0.98	0	0.00	0	0	0.8687	.3513	1.0000	NA	NA	NA
14:07	1	0.49	0	0.00	0	0	0.4329	.5106	1.0000	NA	NA	NA
14:43	1	0.49	0	0.00	0	0	0.4329	.5106	1.0000	NA	NA	NA
14:54	7	3.43	3	3.41	3	6.82	0.0001	.9923	1.0000	0.99 (0.25-3.93)	.9923	.9923
15:01	16	7.84	6	6.82	6	13.64	0.0927	.7608	1.0000	0.86 (0.32-2.28)	.7610	.9923
15:02	2	0.98	11	12.50	10	22.73	19.1789	1.19×10^{-5}	.0001	14.42 (3.13-66.53)	.0006	.0084
16:02	17	8.33	38	43.18	35	79.55	48.8374	2.78×10^{-12}	2.53×10^{-11}	8.36 (4.36-16.04)	1.68×10^{-10}	4.53×10^{-9}

NA, Nonapplicable.

*Number of alleles observed.

†Allele frequencies found in cohort.

‡Number of patients observed.

§Patients frequencies found in cohort.

TABLE E4. The association of HLA-DQB1 alleles with anti-IFN- γ autoantibodies in Taiwan

Allele type	Control (N = 101)		Patient (N = 44)				χ^2	P_{χ^2}	Fisher exact P value	OR (95% CI)	P_{logistic}	P_{FDR}
	Count*	%†	Count*	%†	Carrier‡	%§						
02:01	13	6.37	1	1.14	1	2.27	3.6928	.0546	.0718	0.17 (0.02-1.31)	.0890	.3738
02:02	0	0	1	1.14	1	2.27	2.3261	.1272	.3014	NA	NA	NA
03:01	40	19.61	6	6.82	6	13.64	7.5774	.0059	.0050	0.30 (0.12-0.74)	.0086	.0903
03:02	19	9.31	0	0	0	0	8.7665	.0031	.0013	NA	NA	NA
03:03	35	17.16	6	6.82	6	13.64	5.4446	.0196	.0263	0.35 (0.14-0.87)	.0243	.1276
04:01	12	5.88	12	13.64	10	22.73	4.9001	.0269	.0359	2.53 (1.09-5.87)	.0312	.1456
04:02	2	0.98	2	2.27	2	4.55	0.7600	.3833	.5865	2.35 (0.33-16.94)	.3971	.9811
05:01	7	3.43	10	11.36	9	20.45	7.0552	.0079	.0127	3.61 (1.33-9.82)	.0120	.1008
05:02	25	12.25	42	47.73	36	81.82	43.7541	3.72×10^{-11}	2.21×10^{-10}	6.54 (3.62-11.81)	4.99×10^{-10}	1.05×10^{-8}
05:03	6	2.94	1	1.14	1	2.27	0.8559	.3549	.6788	0.38 (0.04-3.20)	.3728	.9811
06:01	29	14.22	4	4.55	3	6.82	5.7353	.0166	.0156	0.29 (0.10-0.84)	.0233	.1276
06:02	6	2.94	3	3.41	3	6.82	0.0451	.8319	1.0000	1.16 (0.28-4.77)	.8320	.9896
06:03	1	0.49	0	0	0	0	0.4329	.5106	1.0000	NA	NA	NA
06:09	7	3.43	0	0	0	0	3.0938	.0786	.1065	NA	NA	NA
06:10	2	0.98	0	0	0	0	0.8687	.3513	1.0000	NA	NA	NA

NA, Nonapplicable.

*Number of alleles observed.

†Allele frequencies found in cohort.

‡Number of patients observed.

§Patients frequencies found in cohort.

TABLE E5. HLA-DRB1 and -DQB1 alleles with anti-IFN- γ autoantibodies in other regions

Origin	HLA-DRB1		HLA-DQB1	
Hong Kong	15:02	16:02	05:02	05:02
	16:02	16:02	05:02	05:02
	04:05	15:02	03:02	05:02
	03:01	16:02	02:01	05:02
	16:02	16:02	05:02	05:02
	15:01	16:02	05:02	06:01
	09:01	16:02	03:03	05:02
	12:02	16:02	03:01	05:02
The Philippines	04:05	15:02	05:02	05:02
	15:02	15:02	05:02	06:01
	15:02	15:02	05:01	05:02
	15:02	15:02	05:02	05:02
	14:54	15:02	05:02	05:03
	15:02	15:02	05:02	05:02
Vietnam	15:02	15:02	05:01	05:02
	15:01	16:02	05:02	06:01
	09:01	09:01	03:03	03:03
	04:05	16:02	04:02	05:02
Liao	15:02	16:02	05:01	05:02
	14:54	15:02	05:02	05:02
	15:02	15:02	05:01	05:02
United States	15:02	16:02	05:02	05:02
	04:01	13:02	03:01	06:09