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HLA-A33 Is Associated With Susceptibility to Enterovirus 71 Infection

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What's Known on This Subject

Enterovirus 71 has caused large epidemics of disease, resulting in many fatalities and severe sequelae, in Taiwan and some other countries.

What This Study Adds

HLA-A33, which is common in Asian populations but rare in white populations, was most significantly associated with enterovirus 71 infection, compared with the other candidate genes we studied, whereas HLA-A2 was significantly related to cardiopulmonary failure.

ABSTRACT

OBJECTIVE. Enterovirus 71 has caused large epidemics of disease, resulting in many fatalities and severe sequelae, in Taiwan and some other countries. In this study, host genetic factors were investigated to link susceptibility to and clinical severity of enterovirus 71 infections.

METHODS. We enrolled 219 enterovirus 71 case subjects and 97 control children. HLA typing was performed with sequence-specific primers, and polymorphisms of immune-related candidate genes were detected with polymerase chain reaction, followed by automated gene sequencing.

RESULTS. Of the 219 enterovirus 71 cases, 26% (56 of 219 cases) were uncomplicated cases, 74% (163 of 219 cases) were complicated cases, 57% (125 of 219 cases) were complicated cases with central nervous system involvement, and 17% (38 of 219 cases) involved cardiopulmonary failure after central nervous system involvement. Univariate analyses showed that tumor necrosis factor α promoter type II (−308 A allele), HLA-A33, and HLA-DR17 were significantly associated with enterovirus 71 susceptibility. Multivariate analysis demonstrated that HLA-A33 was the gene most significantly susceptible to enterovirus 71. HLA-A2 was associated with the development of cardiopulmonary failure.

CONCLUSIONS. HLA-A33, which is a common phenotype in Asian populations but is rare in white populations, was most significantly associated with enterovirus 71 infection, compared with the other candidate genes we studied, whereas HLA-A2 was significantly related to cardiopulmonary failure. *Pediatrics* 2008;122:1271–1276

SINCE THE TIME it was first recognized in California in 1969,¹ enterovirus 71 (EV71) has caused outbreaks of disease in the United States, Europe, Australia, Japan, Brazil, Malaysia, Taiwan, and elsewhere.^{2–14} Large outbreaks with dozens of fatal cases occurred in Bulgaria in 1975, in Hungary in 1978, and in Malaysia in 1997,^{3,5,9} and the world's largest and most-severe EV71 epidemic occurred in Taiwan in 1998.^{10–14} That epidemic resulted in 129 106 cases of hand, foot, and mouth disease and herpangina, 405 with severe neurologic complications and/or pulmonary edema, and 78 children died.¹⁴ A retrospective review of clinical cases revealed that sporadic cases of EV71 had occurred in Taiwan in 1980 and 1986.^{14,15} With the poliovirus being nearly eradicated and the absence of vaccines and effective antiviral therapies, EV71 may become one of the world's most important enteroviruses and one that could result in many fatalities and serious sequelae.^{14,16}

EV71 can cause fatal diseases. Fatalities are most often attributable to cardiopulmonary failure.^{10,13,14} EV71 also has diverse manifestations, ranging from asymptomatic (~71%) to fatal disease (~0.05%).^{13,17} Why different hosts of the same EV71 infection have different clinical outcomes remains unexplained. In addition to the virulence of the pathogen, genetic factors may be involved in the differences in physical responses to the same infectious agent. Twin

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Key Words

enterovirus 71, HLA-A33, susceptibility

Abbreviations

EV71—enterovirus 71
CNS—central nervous system
TNF- α —tumor necrosis factor α
IL—interleukin
CTL4-4—cytotoxic T lymphocyte-associated antigen 4
PCR—polymerase chain reaction
OR—odds ratio
CI—confidence interval

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studies of tuberculosis, leprosy, malaria, and *Helicobacter pylori* infections found evidence of gene involvement.^{18–21} Another study found a marked increase in the risk of death resulting from infection if the adoptee had a biological parent who died prematurely as a result of infection.²²

To the best of our knowledge, there was no significant association between EV71 viral genotypes and clinical outcomes.^{23,24} A study of host susceptibility and gene resistance to EV71 might be important, especially in Taiwan, where the world's largest epidemic occurred in 1998, as mentioned above, and EV71 continues to circulate, causing severe disease and fatalities.²⁵ To characterize more completely the pathogenesis of EV71 in patients infected with this pathogen, we tested certain immune-related genes and investigated the links between those genetic factors and susceptibility to EV71.

METHODS

EV71 Cases and the Control Group

At Chang Gung Children's Hospital in Taiwan, we enrolled patients with virologically confirmed EV71 illness between May 2001 and April 2003. Institutional review board approval was obtained at Chang Gung Memorial Hospital for this study and informed consent was obtained from the parents of the studied patients.

Virological evaluation included viral isolation from throat and rectal swabs and testing for EV71 IgM and neutralizing antibodies. Virus isolation and serotyping were performed with a traditional cell culture system and fluorescent monoclonal antibody staining (Chemicon International, Temecula, CA). EV71 neutralizing antibody was tested by using the standard protocol of neutralization tests in microtiter plates²⁶; EV71 IgM was measured by using a μ -capture enzyme-linked immunoassay, whose sensitivity and specificity were 91.5% and 93.1%, respectively.²⁷ Virologically confirmed EV71 infection was defined as positive EV71 isolation results, positive EV71 IgM results, EV71 neutralizing antibody four-fold rise or EV71 neutralization antibody seroconversion.

Clinical data, including demographic data, clinical manifestations, disease course, laboratory data, diagnosis, treatment, and clinical outcomes, were recorded. Clinical severity was divided into (1) uncomplicated cases, (2) cases with mild central nervous system (CNS) involvement (aseptic meningitis), (3) cases with severe CNS involvement (including encephalitis, polio-like syndrome, and encephalomyelitis), and (4) cases with cardiopulmonary failure after CNS involvement. Patients with aseptic meningitis experienced headaches, irritability, and cerebrospinal fluid pleocytosis ($>5 \times 10^6$ leukocytes per L) but no altered level of consciousness or focal signs. Patients with encephalitis had an altered level of consciousness plus cerebrospinal fluid pleocytosis, patients with poliomyelitis-like syndrome had acute limb weakness and decreased reflex and muscle strength, and patients with encephalomyelitis had both encephalitis and poliomyelitis-like syndrome. Patients with cardiopulmonary failure after CNS involvement

experienced cardiopulmonary failure 2 to 36 hours (median: 12 hours) after manifestations of EV71 CNS infection; these children all required inotropic agents, endotracheal intubation, and ventilator support, and they had cardiopulmonary failure attributable to medullary damage, without evidence of independent pneumonia, myocarditis, or bacterial sepsis. Clinical outcomes included complete recovery, recovery with sequelae, and death.

For the control group, blood from 7-month-old normal children in our vaccine study was collected, after written informed consent was obtained from parents of each subject, between January 2002 and May 2002. In addition to genotyping of candidate genes, the levels of EV71-neutralizing antibody were measured. These patients had no history of hand, foot, and mouth disease or herpangina, and all of their EV71-neutralizing antibody test results were negative.

Selection of Candidate Genes and Genotyping

Genes Tested

Genomic DNA was extracted from 5 mL of whole blood from both EV71 case subjects and control subjects, with a genomic DNA purification kit (Bioman Scientific, Taipei, Taiwan). On the basis of our previous clinical study, which found elevated levels of prominent inflammatory cytokines, including tumor necrosis factor α (TNF- α), interleukin (IL) 1 β , and IL-6, in EV71 cases with cardiopulmonary failure but not in EV71 cases without cardiopulmonary failure,²⁸ the selected candidate genes were immune-related genes, including the proinflammatory cytokine-related genes (TNF- α promoter, IL-1 β promoter, and IL-6 promoter), cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), and HLA.

TNF- α Promoter

Primers for TNF- α promoter were as follows: sense, 5'-CAAACACAGGCCTCAGGACT-3' (nucleotides -511 to -492); antisense, 5'-GGATACCCCTCACACTCCCC-3' (nucleotides -205 to -224). Polymerase chain reaction (PCR) conditions included an initial denaturation step of 95°C for 5 minutes, 30 cycles of 95°C for 1 minute, 66°C for 1 minute, and 72°C for 1 minute, and finally 72°C for 7 minutes, with a DNA thermal cycler (GeneAmp PCR System 9600; Perkin-Elmer Inc, Waltham, MA).

IL-6 Promoter

Sequencing of the nuclear factor κ B binding site of the IL-6 promoter was performed to detect the single-nucleotide polymorphism at nucleotide -572. The primers were as follows: sense, 5'-GGAATCACACACTCCACC-3' (nucleotides -715 to -698); antisense, 5'-GTGACTGACAGCACAGCT-3' (nucleotides +152 to +135). PCR was performed with an initial denaturation step of 95°C for 5 minutes, followed by 35 cycles of 95°C for 1 minute, 61°C for 1 minute, and 72°C for 1 minute and finally 72°C for 10 minutes.

IL-1 β Promoter

Sequencing of the nuclear factor κ B binding site of the IL-1 β promoter was performed to detect the nucleotide

TABLE 1 Clinical Diagnoses and Outcomes for EV71 Case Subjects

Clinical Diagnosis	n (%)			
	Total	Recovery	Sequelae	Death
Uncomplicated hand, foot, and mouth disease, herpangina, or febrile illness	56 (25.6)	56	0	0
Complicated cases	163 (74.4)			
Aseptic meningitis	97 (44.3)	97	0	0
Severe CNS involvement (encephalitis, encephalomyelitis, or polio-like syndrome)	28 (12.8) ^a	10	18 ^b	0
CNS involvement plus cardiopulmonary failure	38 (17.4)	2	24 ^c	12
Total	219 (100)	165 (75.3)	42 (19.2)	12 (5.5)

^a The 28 patients had severe CNS involvement, including 8 cases of encephalitis, 13 cases of polio-like syndrome, and 7 cases of encephalomyelitis.

^b Seventeen patients had sequelae of limb weakness and atrophy, and 1 had right abducens nerve palsy.

^c There were 19 cases with multiple sequelae of dysphagia, central hypoventilation, and limb weakness/atrophy, 4 with hypoxia-related psychomotor retardation, and 1 with dysphagia alone.

–31 and nucleotide –511 polymorphisms. For the nucleotide –31 polymorphism, the primers were as follows: sense, 5'-AGCTTCCACCAATACTCTTTCCCTTCC-3' (nucleotides –132 to –103); antisense, 5'-TTCACACAAAGAGCAGAGACAGAG-3' (nucleotides +140 to +115). PCR was performed with an initial denaturation step of 95°C for 5 minutes, followed by 38 cycles of 94°C for 1 minute, 60°C for 1 minute, and 72°C for 1 minute and finally 72°C for 7 minutes. For the nucleotide –511 polymorphism, the primers were as follows: sense, 5'-TGGCATTGATCTGGTTCATC-3' (nucleotides –703 to –674); antisense, 5'-GTTTAGGAATCTCCCACTT-3' (nucleotides –399 to –418). PCR was performed with an initial denaturation step of 94°C for 5 minutes, followed by 35 cycles of 94°C for 1 minute, 55°C for 1 minute, and 72°C for 1 minute and finally 72°C for 7 minutes.

CTLA-4

For the nucleotide 49 polymorphism of CTLA-4, the primers included 5'-CCACGGCTTCCTTCTCGTA-3' (nucleotides –208 to –189) and 5'-AGTCTCACTCACCTTTGCAG-3' (nucleotides +121 to +102). PCR was performed with an initial denaturation step of 95°C for 7 minutes, followed by 35 cycles of 95°C for 1 minute, 61°C for 1 minute, and 72°C for 1 minute and finally 72°C for 10 minutes.

Automated DNA Sequencing

After PCR products were purified with the purification kit (Roche Molecular Biochemicals, Indianapolis, IN), automated DNA sequencing was performed with the original primers, an ABI Prism 3100 DNA sequencer, and Genescan 3.1 and Genotyper 3.7 software (Applied Biosystems, Foster City, CA).

HLA Genotyping

PCR with sequence-specific primers was used for HLA genotyping, including HLA class I of HLA-A and HLA-B and HLA class II of HLA-DRB1 and HLA-DRB345, according to the manufacturer's instructions (Micro-SSP HLA class I and class II typing trays; One Lambda, Canoga Park, CA).

Statistical Genetic Analysis

Data were analyzed with SAS/Genetics 9.1 (SAS Institute, Cary, NC). The Hardy-Weinberg equilibrium was tested for each gene, to detect any deviation in the control and EV71 case groups. The genotypic and allelic frequencies of each polymorphism of the genes were compared between the EV71 case group and the control group, to identify the genes associated with EV71 susceptibility, and were compared for EV71 cases with and without cardiopulmonary failure, to identify the genes associated with the development of cardiopulmonary failure, with the Mantel-Haenszel χ^2 test. Then, in multivariate logistic regression models with simultaneous consideration of all significant genotypes and gender, the adjusted odds ratio (OR) and the corresponding 95% confidence interval (CI) for each association were calculated. A *P* value of <.05 was considered significant.

RESULTS

Clinical Diagnoses and Outcomes for EV71 Case Subjects

A total of 219 EV71 cases and 97 control cases were collected. Of the EV71 case subjects, 143 (65%) were male and 76 (35%) were female; of the control children, 46 (47%) were male and 51 (53%) were female (*P* = .003). The clinical syndromes of the 219 EV71 cases were as follows: 56 of the cases (25.6%) were uncomplicated and 163 (74.4%) were complicated; 97 patients (44.3%) had aseptic meningitis, 28 (12.8%) had severe CNS involvement (including 8 cases of encephalitis, 13 cases of polio-like syndrome, and 7 cases of encephalomyelitis), and 38 (17.4%) developed cardiopulmonary failure after CNS involvement (Table 1).

The median duration of follow-up monitoring for the case subjects was 2.9 years (range: 1.0–7.4 years). All of the patients in the uncomplicated cases and the cases with aseptic meningitis recovered completely. Of the 28 patients with severe CNS involvement, 17 had sequelae of limb weakness and atrophy, and 1 had right abducens nerve palsy. Of the 38 patients with cardiopulmonary failure after CNS involvement, 12 children (32%) died, only 2 (5%) recovered completely, and 24 (63%) had sequelae, including 19 with multiple sequelae of dyspha-

TABLE 2 TNF- α Promoter, IL-6 Promoter, IL-1 β Promoter, and CTLA-4 Polymorphisms in Case Subjects and Normal Control Subjects

Polymorphism of Candidate Gene	n (%)		P	OR (95% CI)
	Case (N = 219)	Control (N = 97)		
TNF- α promoter				
–308 with A allele	56 (26)	14 (14)	.02	2.12 (1.11–4.02)
–376 with A allele	2 (1)	0	.34	NA
–238 with A allele	6 (3)	3 (3)	.86	0.88 (0.22–3.67)
IL-6 promoter, –572 with G allele	80 (38)	40 (41)	.56	0.86 (0.53–1.41)
IL-1 β promoter				
–31 with C allele	166 (76)	68 (71)	.20	1.42 (0.83–2.46)
–511 with T allele	159 (74)	80 (82)	.11	0.61 (0.34–1.13)
CTLA-4, +49 with A allele	106 (48)	50 (52)	.74	0.92 (0.57–1.49)

NA indicates not applicable.

gia, central hypoventilation, and limb weakness/atrophy, 4 with hypoxia-related psychomotor retardation, and 1 with dysphagia alone (Table 1).

Polymorphisms of TNF- α Promoter, IL-6 Promoter, IL-1 β Promoter, and CTLA-4 in the EV71 Case and Normal Control Groups

The allelic and genotypic distributions of the TNF- α promoter, IL-6 promoter, IL-1 β promoter, and CTLA-4 among the control subjects, as well as the EV71 case subjects, did not differ significantly from Hardy-Weinberg equilibrium. Table 2 shows the polymorphisms of the candidate genes for the TNF- α promoter, IL-6 promoter, IL-1 β promoter, and CTLA-4 among the EV71 case subjects and the normal control children. Only the TNF- α promoter with the nucleotide –308 A allele (TNF- α type II promoter) was found to have a higher incidence among EV71 case subjects than among normal control children (OR: 2.12; 95% CI: 1.11–4.02; P = .02).

HLA Genotyping in the EV71 Case and Normal Control Groups

Results of the class I and class II HLA genotyping with sequence-specific primers are shown in Table 3. For class I HLA, the incidence of HLA-A33 in the EV71 case subjects (30%; 65 of 219 children) was significantly greater than that for normal children (14%; 14 of 97 children; OR: 2.50; 95% CI: 1.33–4.73; P = .004). For class II HLA, the incidence of HLA-DR17 in the EV71 case subjects (24%; 53 of 219 children) was significantly greater than that in normal children (11%; 11 of 97 children; OR: 2.5; 95% CI: 1.25–5.06; P = .008) (Table 3).

Multivariate Analysis for the Susceptible Genes in EV71 Infection

Because TNF- α type II promoter, HLA-A33, HLA-B58, and HLA-DR17 were found to be significantly associated with EV71 infection in univariate analyses, multivariate analysis was performed. There was a gender difference between case and control subjects; therefore, gender was included in the multivariate analysis as a confounder. After gender adjustment, the analysis revealed HLA-A33

TABLE 3 HLA Class I and Class II Genotypes for Case Subjects and Normal Control Subjects

Genotype	n (%)		P	OR (95% CI)
	Case (N = 219)	Control (N = 97)		
HLA-A				
A33	65 (30)	14 (14)	.004	2.50 (1.33–4.73)
A11	119 (54)	60 (62)	.21	0.73 (0.45–1.20)
A24	64 (29)	32 (33)	.50	0.84 (0.50–1.40)
A26	12 (5)	2 (2)	.17	2.75 (0.60–12.55)
A31	9 (4)	2 (2)	.36	2.04 (0.43–9.60)
A2	104 (47)	52 (54)	.32	0.78 (0.49–1.26)
HLA-B				
B58	60 (27)	17 (18)	.06	1.78 (0.97–3.24)
B75	25 (11)	11 (11)	.98	1.01 (0.47–2.14)
B46	48 (22)	17 (18)	.37	1.32 (0.72–2.44)
B13	31 (14)	15 (15)	.76	0.90 (0.46–1.76)
B60	93 (42)	37 (38)	.47	1.20 (0.73–1.95)
B54	16 (7)	5 (5)	.48	1.45 (0.52–4.08)
B62	19 (9)	12 (12)	.31	0.67 (0.31–1.45)
B27	15 (7)	6 (6)	.83	1.12 (0.42–2.97)
B51	18 (8.2)	5 (5)	.33	1.65 (0.59–4.57)
B35	10 (4.6)	8 (8)	.19	0.53 (0.20–1.39)
B55	13 (5.9)	5 (5)	.78	1.16 (0.40–3.35)
B52	6 (3)	4 (4)	.52	0.66 (0.18–2.38)
DRB1				
DR17	53 (24)	11 (11)	.008	2.51 (1.25–5.06)
DR15	35 (16)	21 (22)	.23	0.69 (0.38–1.27)
DR8	38 (17)	20 (21)	.50	0.81 (0.44–1.49)
DR12	63 (29)	23 (24)	.34	1.31 (0.75–2.27)
DR13	11 (5.1)	6 (6)	.68	0.81 (0.29–2.25)
DR14	27 (12)	11 (11)	.79	1.11 (0.52–2.33)
DR11	35 (16)	19 (20)	.44	0.79 (0.42–1.46)
DR16	14 (6.4)	6 (6)	.94	1.04 (0.39–2.79)
DR7	12 (5.5)	4 (4)	.61	1.35 (0.43–4.31)
DR4	64 (29)	30 (31)	.78	0.93 (0.55–1.56)
DR9	59 (27)	19 (20)	.16	1.52 (0.85–2.73)
DR10	5 (2)	2 (2)	.89	1.13 (0.22–5.91)

TABLE 4 Multivariate Analysis for Susceptible Genes for EV71 Infections Among Immunoregulatory Genes

Gender/Gene	n (%)		P	Adjusted OR (95% CI)
	Case (N = 219)	Control (N = 97)		
Male gender	143 (65)	46 (47)	.001	2.27 (1.38–3.70)
TNF- α type II promoter	56 (26)	14 (14)	.95	1.04 (0.26–4.16)
HLA-A33	65 (30)	14 (14)	.02	2.96 (1.20–7.34)
HLA-B58	60 (27)	17 (18)	.24	0.40 (0.08–1.89)
HLA-DR17	53 (24)	11 (11)	.06	3.10 (0.97–9.87)

to be most significantly associated with EV71 infection (OR: 2.96; 95% CI: 1.20–7.34; P = .02) (Table 4).

Genes Associated With EV71-Related Cardiopulmonary Failure

Of all the candidate genes we studied, only HLA-A2 was associated with the development of EV71 cardiopulmonary failure among EV71 case subjects. EV71 case subjects with cardiopulmonary failure had higher rates of HLA-A2 (63%; 24 of 38 children) than did EV71 case subjects without cardiopulmonary failure (44%; 80 of

181 children; OR: 2.16; 95% CI: 1.05–4.44; $P = .03$). In contrast, the IL-1 β promoter with the nucleotide –511 T allele was associated with less likelihood of developing cardiopulmonary failure (OR: 0.45; 95% CI: 0.22–0.95; $P = .03$).

DISCUSSION

Our results show that HLA-A33 significantly influences susceptibility to EV71 infection. In addition, among the EV71 case subjects, HLA-A2 was related to the development of cardiopulmonary failure after CNS involvement. These findings provide some evidence of associations between host genetic factors and susceptibility to EV71 and clinical severity.

Genetic variations in the immune system are known to be related to susceptibility and clinical outcomes of various infections. For example, the highly polymorphic HLA genes are increasingly recognized as a correlate of susceptibility to or severity of some infections, including malaria,²⁹ tuberculosis,³⁰ HIV infection,³¹ and hepatitis B.³² The functional role of HLA is to present antigens to the immune system, and the extraordinary genetic diversity of HLA is postulated to have arisen as a host strategy to counter antigenic diversity in infectious organisms. In this study, we found HLA-A33 to be the most significant gene associated with EV71 susceptibility. HLA-A33 has been found to be very rare, with a phenotypic frequency of 0% to 1%, in white populations, including the US white population, whereas the phenotypic frequency of HLA-A33 is reported to be ~17% to 35% in Asian populations, including Taiwanese, Japanese, Singapore, and Malaysian peoples.^{33–35} For the 2 countries with the majority of fatal EV71 cases in the past 10 years, the allelic frequencies of HLA-A33 were very close, that is, 11.6% in Taiwan and 12.9% in Malaysia.^{34,35} This may explain why EV71 outbreaks occur much more frequently in Asian countries than in Western countries.²⁵ Very little is known about the role of HLA in EV71 infection, and additional investigation is needed to determine whether the major histocompatibility complex serves as a specific receptor for EV71 infection.

A polymorphism of another immunoregulatory gene, TNF- α promoter (a key mediator of fever and the inflammatory response to infection), has been associated with higher mortality rates and morbidity rates for bacterial sepsis,³⁶ and this polymorphism also has been associated with the severity of malaria, leishmaniasis, and leprosy.^{37,38} In a previous study, we demonstrated elevated levels of prominent inflammatory cytokines, such as TNF- α , IL-1 β , and IL-6, in fatal EV71 cases but not in nonfatal cases,²⁸ and such cytokine responses were similar to those in bacterial sepsis. In this study, we found that TNF- α promoter type II was associated with EV71 susceptibility in univariate analyses but was not associated with clinical severity. A previous study showed that polymorphism of CTLA-4 at position 49 showed a higher frequency of the G/G genotype in patients with EV71 meningoencephalitis than in patients without meningoencephalitis (18 of 31 patients vs 14 of 47 patients; $P = .045$) or control subjects (18 of 31 patients vs 25 of 931

subjects; $P = .007$).³⁹ This study showed different results, however; the frequencies of the G/G genotype of CTLA-4 at position 49 were similar between the EV71 and control groups (108 of 214 patients vs 47 of 97 subjects; $P = .50$), and the patients with meningoencephalitis did not have a higher frequency of the G/G genotype than did the control subjects (63 of 120 patients vs 47 of 97 subjects; $P = .77$).

This study found HLA-A2 to be correlated with the development of cardiopulmonary failure after CNS involvement. HLA-A2.1 was found to present a 9-mer peptide epitope from the 2C nonstructural protein of coxsackievirus B4, and the epitope is recognized by effector memory CD8⁺ T cells; therefore, it may play some role in the pathogenesis of the autoimmune disease type 1 diabetes mellitus.⁴⁰ The role of HLA-A2 in the pathogenesis of EV71-related cardiopulmonary failure remains unclear. In our previous study, we found that EV71-specific cell-mediated immunity was significantly lower in cases with cardiopulmonary failure than in other EV71 cases.⁴¹ Additional investigation is needed to determine whether the specific HLA may affect patients' EV71-specific cell-mediated immunity, resulting in varying clinical severity.

CONCLUSIONS

This study found significant relationships between HLA-A33 and host susceptibility to EV71 and between HLA-A2 and the development of EV71-related cardiopulmonary failure. HLA-A33 is found more frequently in Asian populations than in white populations, which may explain why EV71 outbreaks occur more frequently in Asian countries, in this case Taiwan.

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