HLA class I supertype associations with clinical outcome of secondary dengue virus infections in ethnic Thais

HLA class I supertype associations with clinical outcome of secondary dengue virus infections in ethnic Thais

IF = 5.778

MAJOR ARTICLE

HLA Class I Supertype Associations With Clinical Outcome of Secondary Dengue Virus Infections in Ethnic Thais

Sasijit Vejbaesya,[1] Rungrot Thongpradit,[1] Siripen Kalayanarooj,[2] Komon Luangtrakool,[1] Panpimon Luangtrakool,[1] Robert V. Gibbons,[3] Duangporn Srinak,[1] Somporn Ngammthaworn,[1] Kusuma Apisawes,[1] In-Kyu Yoon,[3] Stephen J. Thomas,[4] Richard G. Jarman,[4] Anon Srikiakthachorn,[5] Sharone Green,[5] Dasnayanee Chandanayingyong,[1] Sangshin Park,[6] Jennifer Friedman,[6] Alan L. Rothman,[7] and Henry A.F. Stephens[1,8]

[1]Department of Transfusion Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, [2]Queen Sirikit National Institute of Child Health, [3]Department of Virology, Armed Forces Research Institute of Medical Science, Bangkok, Thailand; [4]Viral Diseases Branch, Walter Reed Army Institute of Research, Silver Spring, Maryland; [5]Division of Infectious Diseases and Immunology, Department of Medicine, University of Massachusetts Medical School, Worcester; [6]Center for International Health Research, Rhode Island Hospital, The Warren Alpert Medical School of Brown University, [7]Institute for Immunology and Informatics, University of Rhode Island, Providence; and [8]UCL Centre for Nephrology and Anthony Nolan Laboratories, Royal Free NHS Foundation Trust, Royal Free Hospital, London, United Kingdom

Background. Human leukocyte antigen (HLA) supertypes are groups of functionally related alleles that present structurally similar antigens to the immune system.

Objectives. To analyze HLA class I supertype associations with clinical outcome in hospitalized Thai children with acute dengue illness.

Methods. Seven hundred sixty-two patients and population-matched controls recruited predominantly in Bangkok were HLA-A and -B typed. HLA supertype frequencies were compared and tested for significant dengue disease associations using logistic regression analyses. Multivariable models were built by conducting forward stepwise selection procedures.

Results. In the final logistic regression model, the HLA-B44 supertype was protective against dengue hemorrhagic fever (DHF) in secondary infections (odds ratio [OR] = 0.46, 95% confidence interval [CI], .30–.72), while the HLA-A02 supertype (OR = 1.92, 95% CI, 1.30–2.83) and the HLA-A01/03 supertype (OR = 3.01, 95% CI, 1.01–8.92) were associated with susceptibility to secondary dengue fever. The B07 supertype was associated with susceptibility to secondary DHF in the univariate analysis (OR = 1.60, 95% CI, 1.05–2.46), whereas that was not retained in the final model.

Conclusions. As the HLA-B44 supertype is predicted to target conserved epitopes in dengue, our results suggest that B44 supertype-restricted immune responses to highly conserved regions of the dengue proteome may protect against secondary DHF.

Keywords. HLA; class I; B44; supertype; associations; secondary; dengue; infections; Thais.

HLA class I supertype associations with clinical outcome of secondary dengue virus infections in ethnic Thais

Assoc.Prof.Dr.Sasijit Vejbaesya
Department: Transfusion Medicine
Field of interests: Transplantation Immunologic
Contribution: Correspondent author

Rungrot Thongpradit
Department: Transfusion Medicine
Field of interests: Transplantation Immunologic
Contribution: Co-author

Panpimon Luangtrakool
Department: Transfusion Medicine
Field of interests: transplantation Immunologic
Contribution: Co-author

Somporn Ngammthaworn
Department: Transfusion Medicine
Field of interests: transplantation Immunologic
Contribution: Co-author

Komon Luangtrakool
Department: Transfusion Medicine
Field of interests: transplantation Immunologic
Contribution: Co-author

Kusuma Apisawes
Department: Transfusion Medicine
Field of interests: Transplantation Immunologic
Contribution: Co-author

Dasnayanee Chandanayingyong
Department: Transfusion Medicine
Field of interests: transplantation Immunologic
Contribution: Co-author

HLA class I supertype associations with clinical outcome of secondary dengue virus infections in ethnic Thais

- **HLA-A Supertypes**

Table 1. HLA-A Supertype Frequencies in Bangkok Thai Dengue Patients and Controls

			Supertype Frequency (SF%)			
			Primary Infection	Secondary Infection		Control
HLA Class I Supertype	HLA-A Locus Alleles in Thais	Recognized Supermotif in Target Antigens	DF N = 77 n = (SF)	DF N = 200 n = (SF)	DHF N = 150 n = (SF)	N = 227 n = (SF)
A01	*A*01* *A*26* *A*32*	Pos 2: Small aliphatic (Ala, Thr, Ser, Val, Leu, Iso, Met, Gln) Pos 9/10: Aromatic and large hydrophobic (Phe, Trp, Tyr, Leu, Iso, Met)	7 (9%)	11 (6%)	14 (9%)	23 (10%)
A02	*A*02*	Pos 2: Small aliphatic (Ala, Thr, Ser, Val, Leu, Iso, Met, Gln) Pos 9/10: Aliphatic and small hydrophobic (Leu, Iso, Val, Met, Gln, Ala)	36 (47%)	**105 (53%) *A,*C**	**75 (50%) *B,*C**	**85 (37%) *A, *B, *C**
A03	*A*03* *A*11* *A*31* *A*33*	Pos 2: : Small aliphatic (Ala, Thr, Ser, Val, Leu, Iso, Met, Gln) Pos 9/10: Basic (Arg, His, Lys)	57 (74%)	149 (75%)	99 (66%)	170 (75%)
A24	*A*24*	Pos 2: Aromatic and aliphatic (Phe, Trp, Tyr, Leu, Iso, Val, Met, Gln) Pos 9/10: Aromatic, aliphatic and hydrophobic (Phe, Try, Tyr, Leu, Ile, Met, Val, Ala)	32 (42%)	65 (33%)	63 (42%)	82 (36%)
A01/A03	*A*30*	Pos 2: Small and aliphatic (Ala, Thr, Ser, Val, Leu, Iso, Met, Gln) Pos 9/10: Aromatic and basic (Tyr, Arg, Lys)	1 (1%)	11 (6%)	4 (3%)	5 (2%)
A01/A24	*A*29*	Pos 2: Small, aliphatic and aromatic (Ala, Ser, Thr, Val, Leu, Ile, Met, Gln, Phe, Trp, Tyr) Pos 9/10: Aromatic and large hydrophobic (Phe, Trp, Tyr, Leu, Iso, Met)	. . .	3 (2%)	3 (2%)	3 (1%)
UC	*A*34*	Unknown	2 (3%)	4 (2%)	2 (1%)	3 (1%)
Wald χ^2			***P* =**	P_c=	**OR**	**95% CI**
*A A2 SF% in secondary DF infections vs controls, $W\chi^2 = 9.7$			**.0019**	**0.0266**	**1.85**	**1.26–2.72**
*B A2 SF% in secondary DHF infections vs controls, $W\chi^2 = 5.8$			**.0161**	0.2254	**1.67**	**1.10–2.54**
*C A2 SF% in all secondary infections (DF and DHF) vs controls, $W\chi^2 = 10.8$			**.0010**	**0.0140**	**1.77**	**1.26–2.49**

The preferred supermotif amino acids held in the B and F pockets of the HLA class I antigen binding clefts of A02 supertype alleles, together with the A02 supertype alleles identified in our Thai cohort

HLA class I supertype associations with clinical outcome of secondary dengue virus infections in ethnic Thais

- **HLA-B Supertypes**

Table 2. HLA-B Supertype Frequencies in Bangkok Thai Dengue Patients and Controls

			Supertype Frequency (SF%)			
			Primary Infection	Secondary Infection		Control
HLA Class I Supertype	HLA-B Locus Alleles in Thais	Recognized Supermotif in Target Antigens	DF N = 77 n = (SF)	DF N = 200 n = (SF)	DHF N = 150 n = (SF)	N = 227 n = (SF)
B07	*B*07 B*35 B*51 B*54 B*55 B*56 B*67*	Pos 2: Proline Pos 9/10: Aromatic, aliphatic and hydrophobic (Phe, Try, Tyr, Leu, Ile, Met, Val, Ala)	27 (35%)	**76 (38%) *B**	**64 (43%) *A,*B**	**72 (32%) *A,*B**
B08	*B*08*	Pos 2: undefined Pos 9/10: Aromatic, aliphatic and hydrophobic (Phe, Try, Tyr, Leu, Ile, Met, Val, Ala)	. . .	2 (1%)	. . .	3 (1%)
B27	*B*27 B*38 B*39 B*48*	Pos 2: Basic (Arg, His, Lys) Pos 9/10: Aromatic, aliphatic, basic and hydrophobic (Phe, Try, Trp, Leu, Ile, Met, Arg, His, Lys, Val, Ala)	13 (17%)	50 (25%)	35 (23%)	48 (21%)
B44	*B*18 B*37 B*40 B*44 B*50*	Pos 2: Acidic (Asp, Glu) Pos 9/10: Aromatic, aliphatic and hydrophobic (Phe, Trp, Tyr, Leu, Ile, Val, Met, Gln, Ala)	29 (38%)	**80 (40%) *C,*E**	**40 (27%) *C,*D, *E**	**100 (44%) *D,*E**
B58	*B*15:17 B*57 B*58*	Pos 2: Small (Ala, Ser, Thr) Pos 9/10: Aromatic, aliphatic and hydrophobic (Phe, Trp, Tyr, Leu, Ile, Val, Met, Gln, Ala)	12 (16%)	24 (12%)	28 (19%)	40 (18%)
B62	*B*15:01 B*15:02 B*15:12 B*15:13 B*15:25 B*46 B*52*	Pos 2: Aliphatic (Leu, Iso, Val, Met, Gln) Pos 9/10: Aromatic, aliphatic and hydrophobic (Phe, Trp, Tyr, Leu, Ile, Val, Met, Gln, Ala)	43 (56%)	95 (48%)	77 (51%)	121 (53%)
UC	*B*13 B*15:21 B*15:27 B*15:32*	Unconfirmed	13 (17%)	36 (18%)	24 (16%)	31 (14%)

Wald χ^2	***P* =**	P_c=	**OR**	**95% CI**
*A B07 SF% in secondary DHF infections vs controls, **Wχ^2 = 4.7**	**.0307**	0.4298	**1.60**	**1.05–2.46**
*B B07 SF% in all secondary infections (DF and DHF) vs controls, **Wχ^2 = 4.0**	**.0442**	0.6188	**1.44**	**1.01–2.04**
*C B44 SF% in secondary DHF vs secondary DF infections, **Wχ^2 = 6.7**	**.0097**	0.1358	**0.55**	**.35–.86**
*D B44 SF% in secondary DHF vs controls, **Wχ^2 = 11.5**	**.0007**	**0.0098**	**0.46**	**.30–.72**
*E B44 SF% in all secondary infections (DF and DHF) vs controls, **Wχ^2 = 5.5**	**.0185**	0.2590	**0.66**	**.47–.93**

modest association between the B07 supertype and susceptibility to DHF in patients with secondary infections

most significant association detected was with the B44 supertype and protection against developing severe DHF in secondary DENV infections, when compared to secondary DF patients and the controls

HLA class I supertype associations with clinical outcome of secondary dengue virus infections in ethnic Thais

- **Logistic Regression Model**

To investigate whether the evaluated HLA class I supertypes were related to either increased or decreased risk of primary/secondary DF or secondary DHF versus controls

Table 3. Logistic Regression Models for HLA Class I Supertype Associations With Dengue Virus Infection

Secondary DENV Infection	HLA Class I Supertype	OR vs Controls	95% CI	*P* Value
DF	A02	1.92	1.30–2.83	.0011
	A01/A03	3.01	1.01–8.92	.0474
DHF	B44	0.46	.30–.72	.0007

Abbreviations: CI, confidence interval; DENV, dengue virus; DF, dengue fever; DHF, dengue hemorrhagic fever; HLA, human leukocyte antigen; OR, odds ratio.

the presence of one did not significantly modify or change the relationship of the other supertype to secondary DF and DHF

HLA class I supertype associations with clinical outcome of secondary dengue virus infections in ethnic Thais

- **B44 Supertype Protects Against Secondary DHF With All Four DENV Serotypes**

Table 4. Logistic Regression Analysis of HLA-B44 Supertype Frequencies in Secondary DENV-1, DENV-2, DENV-3, or DENV-4 Infections in Bangkok Thais

	DENV Serotype Identified in Secondary Infections								
	DENV-1		DENV-2		DENV-3		DENV-4		Control
	DF N = 74 n = (SF)	DHF N = 50 n = (SF)	DF N = 40 n = (SF)	DHF N = 39 n = (SF)	DF N = 42 n = (SF)	DHF N = 37 n = (SF)	DF N = 42 n = (SF)	DHF N = 21 n = (SF)	N = 227 n = (SF)
HLA B44 Supertype	32 (43%)	12 (24%)	14 (35%)	11 (28%)	18 (43%)	11 (30%)	15 (36%)	5 (24%)	100 (44%)
OR (95% CI) Patient Groups vs Controls (ref)	0.97 (.57–1.64)	**0.40 (.20–0.81)**[a]	0.68 (.34–1.38)	0.50 (.24–1.05)	0.95 (.49–1.85)	0.54 (.25–1.14)	0.71 (.36–1.40)	0.40 (.14–1.12)	Ref
Wald χ^2–derived *P* Value	.9031	**.0105**	.2877	.0675	.8862	.1056	.3172	.0809	
OR (95% CI) DHF vs DF (ref) within given DENV serotype	Ref	**0.41 (.19–.92)**[a]	Ref	0.73 (.28–1.89)	Ref	0.56 (.22–1.43)	Ref	0.56 (.17–1.84)	
Wald χ^2–derived *P* Value		**.0300**		.5168		.2291		.3419	

HLA class I supertype associations with clinical outcome of secondary dengue virus infections in ethnic Thais

- **B44 Supertype Protects Against the Most Severe Forms of DHF**

Table 5. Logistic Regression Analysis of HLA B44 Supertype Associations With Severe Secondary Dengue Infections in Bangkok Thais

	HLA-B44 Supertype Frequency (SF%) in Patients With Secondary Dengue and Controls				
	Secondary DF	Secondary DHF-1	Secondary DHF-2	Secondary DHF-3/4	Control
	N = 200 n = (SF)	N = 22 n = (SF)	N = 96 n = (SF)	N = 32 n = (SF)	N = 227 n = (SF)
HLA B44 Supertype	80 (40%)	7 (32%)	28 (29%)	5 (16%)	100 (44%)
OR (95% CI) Patient Groups vs controls (ref)	0.85 (.58–1.25)	0.59 (.23–1.51)	**0.52 (.31–.87)**[a]	**0.24 (.09–.63)**[a]	Ref
Wald χ^2–derived *P* Value	.3975	.2727	**.0131**	**.0041**	
OR (95% CI) DHF vs DF (ref)	Ref	0.70 (.27–1.79)	0.62 (.37–1.04)	**0.28 (.10–.75)**[a]	
Wald χ^2–derived *P* Value		.4574	.0711	**.0117**	

The most frequent B44 supertype-related alleles in our Thai cohort were HLA-B*40, B*18, and B*44, which were all relatively reduced in frequency in the secondary DHF patients

- **SUMMARY**

B44 supertype associations described in Tables 2–5 are not due to relatively increased or decreased frequencies of any particular B44-related allele