Distribution of Human Leukocyte Antigens-E Alleles in Thailand

INGORN KIMKONG, BSc*,
APIWAT MUTIRANGURA, MD, PhD**,
NATTIYA PIMTANOTHAI, MD, PhD***

Abstract

The aim of this study was to investigate the distribution of human leukocyte antigens (HLA) -E alleles in Thailand. HLA-E alleles were assigned by using a polymerlase chain reaction-sequence specific oligonucleotide probes (PCR-SSOP) method and direct sequencing in 200 healthy individuals. They comprised 100 Thai, 50 Chinese and 50 Thai-Chinese. From the results, three alleles of HLA-E could be detected in these populations. The E*0101 was the most common allele in Thai and Thai-Chinese with allelic frequencies of 42.5 per cent and 38 per cent, respectively. The other HLA-E allele frequencies of Thai origin were 33 per cent for E*01031 and 24.5 per cent for E*01032, respectively. Among Thai-Chinese, the allele frequencies of HLA-E were 31 per cent for E*01031 and E*01032, respectively. Whereas, the E*01031 was the predominant allele in Chinese origin with a frequency of 39 per cent, followed by E*0101 and E*01032 with 32 per cent and 29 per cent, respectively. No E*01033, E*0102 and E*0104 could be detected in all individuals. When comparing the distribution of HLA-E alleles between each of the populations (Thai *vs* Chinese, Thai *vs* Thai-Chinese and Chinese *vs* Thai-Chinese), no significant difference could be found among these populations. In addition, there was no significant difference of the distribution of HLA-E alleles between the study populations and other populations from Asian countries, reported previously. However, there were significant differences between the populations (Thai, Chinese and Thai-Chinese) and Danish ($\chi^2 = 15.64$, $p = 0.0004$; $\chi^2 = 24.58$, $p = 0.0000046$; $\chi^2 = 14.69$, $p = 0.00065$, respectively).

Key word : HLA-E, Alleles, PCR-SSOP, Direct Sequencing

KIMKONG I, MUTIRANGURA A, PIMTANOTHAI N
J Med Assoc Thai 2003; 86 (Suppl 2): S230-S236

* Inter-Department of Medical Microbiology, Graduate School,
** Department of Anatomy, Faculty of Medicine,
*** Department of Microbiology, Faculty of Medicine Chulalongkorn University, Bangkok 10330, Thailand.

HLA-E belongs to non-classical HLA class Ib whose molecules are homologous to classical HLA class Ia molecule[1]. HLA-E is located between HLA-A and -C on the short arm of chromosome 6[2]. Transcripts of this gene have been found in a wide variety of different tissues[3]. HLA-E has been found to present class I leader peptides and to be recognized by natural killer cells[4,5]. This recognition is mediated by the interaction of HLA-E with the CD94/NKG2 receptor and can result in either inhibition or activation of the natural killer cell, depending on the peptide presented and which NKG2 receptor it associates with[4,6,7]. In addition, several observations raise the possibility that HLA-E might play an important role in the regulation of cytotoxic T. lymphocyte (CTL) function, as CD94/NKG2 receptors are expressied on a subset of CTL cell function[8,9]. In addition, there is evidence that HLA-E can interact with T cell receptors (TCRs). The data imply the generation of human T cells potentially recognized through the αβTCR-HLA-E molecules that bind to class I- and virus-derived peptides[10]. One indirect evidence included the observation that Qa-1b, a mouse homologue of HLA-E has been proposed to present H-2-unrelated antigenic peptides that may be specifically recognized by T lymphocytes[11-15]. Although the precise functions of the HLA-E gene have yet to be fully elucidated, it does appear that these gene products play vital roles in immune function.

The HLA-E gene differs from the class Ia genes with respect to the number of alleles present at each locus. In comparison to the highly polymorphic class Ia genes[16], the class Ib genes appear to show much less, if any, allelic variation[2]. There are six HLA-E alleles currently registered (http://www3.Ebi.ac.uk/services/imgt/hla/cgi-bin/align.cgi) containing both synonymous and nonsynonymous substitutions and designated HLA-E*0101, *0102, *01031, *01032, *01033 and *0104 (Table 1). The polymorphism is based on four nucleotide substitutions in exon 2 and three in exon 3 (Table 1) reported by several authors [17-21]. The importance of the different of HLA-E alleles in transplant rejection and disease susceptibility has been proposed. However, there are still few population studies for the distribution of HLA-E alleles in various populations. The aim of this study was to investigate the distribution of HLA-E alleles in Thailand by direct sequencing and PCR-SSOP typing method.

MATERIAL AND METHOD

Study population

After having obtained the subjects' informed consent as to the purpose of the study blood samples

Table 1. Nucleotide and deduces amino acid substitution characterizing the HLA-E alleles.

Nucleotide positions	Exon 2 α-1 domain [a]				Exon 3 α-1 domain [b]		
	5	230	245	246	48	179	198
0101	C	C	C	G	A	C	A
0102	C	C	G [c]	C	A	C	A
01031	C	C	C	G	G	C	A
01032	C	T [c]	C	G	G	C	A
01033	C	C	C	C	G	T [c]	C
0104	T [c]	C	C	G	G	C	G
Amino acid position	**Exon 2 α-1 domain [a]**				**Exon 3 α-1 domain [b]**		
	2	77	82	83	107	150	157
0101	Ser	Asn	Arg	Gly	Arg	Ala	Arg
0102	Ser	Asn	Arg	Arg	Arg	Ala	Arg
01031	Ser	Asn	Arg	Gly	Gly	Ala	Arg
01032	Ser	Asn	Arg	Gly	Gly	Ala	Arg
01033	Ser	Asn	Arg	Gly	Gly	Ala	Arg
0104	Ser	Asn	Arg	Gly	Gly	Ala	Gly

[a] Codon 1 to 91, nucleotide 1 to 270
[b] Codon 91 to 183, nucleotide 1 to 276
[c] not reflected in amino acid substitution

were collected by venipuncture. This study was approved by The Ethics Committee of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Two hundred healthy unrelated individuals were recruited from the National Blood Center, the Thai Red Cross Society. They were permanent residents in Bangkok or the central part of Thailand. All individuals were interviewed and then divided into three groups, Thai, Chinese and Thai-Chinese, respectively, based on the ethnic origins of their grandparents. If their ancestors, including their great grandparents, originated from China, they were considered Chinese. On the other hand, if their ancestors originated from Thailand, they were defined as Thai. In addition, if their ancestors originated from Thailand and China, they were defined as Thai-Chinese. The healthy individuals comprised 100 Thai, 50 Chinese and 50 Thai-Chinese. The age range was 18-59 years (mean 34.7).

DNA extraction and PCR amplification of the HLA-E gene

Molecular genetic analysis was performed on genomic DNA, obtained from peripheral blood using standard phenol-chloroform extraction procedure as previously described[22]. The genomic DNA were amplified with the use of the HLA-E gene specific primers HLA-E.2F [5' GAA ACG GCC TCT ACC GGG AGT AG 3'] and HLA-E.2R [5' GTT CCG CAG CCT TGG GGT GAA TC 3'] described by Hodgkinson AD et al which is specifically amplify exon 2[23]. While primers HLA-E.3F [5' CGG GAC TGA CTA AGG GGC 3'] and HLA-E.3R [5' AGC CCT GTG GAC CCT CTT 3'] described by Gomez-Casoda EG et al specifically amplify exon 3[19]. The reaction volume for the amplification reaction was 50 µl, containing 50 ng/µl genomic DNA, 0.25 µl of 5.0 U Taq polymerase (Promega or Gibco, USA), 5 µl of 10x PCR buffer (20mM Tris-HCl pH 8.0, 100 mM KCl), 3 µl of 25 mM $MgCl_2$, 1 µl of 10 mM deoxynucletide triphosphates and 2.5 µl (20 pmol) of each primer. Amplification was performed in Perkin Elmer/GeneAmp PCR system 2400 or Applied Biosystems/GeneAmp PCR system 9600 (USA). The PCR protocol consisted of an initial denaturation at 94°C for 2 minutes, followed by 30 cycles of denaturation (94°C, 20 seconds), annealing (58°C, 50 seconds) and extension (72∞c, 20 seconds) and final extension at 72°C for 7 minutes. The resulting products were further analyzed by 1.5 per cent agarose gel electrophoresis.

Dot-blot hybridization

Twelve SSOPs (Sequence specific oligonucleotide probes) were used for oligotyping of HLA-E alleles as shown in Table 2. Ten SSOPs previously described by Gomez-Casado E et al[19]. Two SSOPs of codon150C/T were designed in this study. The SSOPs were labeled with γ-^{32}P-adenosine triphosphate (ATP) (Amersham, England) and T4 polynucleotide kinase (New English BioLab, USA). PCR products were spotted onto nylon membrane (Hybond-N; Amercham, England), immobilized by denaturing solution [1.5 M NaCl and 0.5 M NaOH] and neutralized with neutralizing solution [1.5 NaCl, 0.5 M Tris-HCl (pH 7.2) and 0.5 M EDTA (pH 8.0)]. Prehybridization of the membrane was performed in a hybri-

Table 2. SSOPs used for oligotyping of HLA-E alleles.

	Probe	Codon	Sequence (5' → 3')	HLA-E specificities
Exon 2	E2011	2	GGCTCCCACTCCTTG	0101, 0102, 01031, 01032, 01033
	E2012		GGCTCTCACTCCTTG	0104
	E2021	77	CGAGTGAACCTGCGG	0101, 0102, 01031, 0104
	E2022		CGAGTGAATCTGCGG	01032, 01033
	E2031	82, 83	CTGCGCGGCTACTAC	0101, 01031, 01032, 01033, 0104
	E2032		CTGCGGCGCTACTAC	0102
Exon 3	E3011	107	CCCGACAGGCGCTTC	0101, 0102
	E3012		CCCGACGGGCGCTTC	01031, 01032, 01033, 0104
	150C	150	GATGCCTCTGAGGCG	0101, 0102, 01031, 01032, 0104
	150T		GATGCTTCTGAGGCG	01033
	E3021	157	CACCAGAGAGCCTAC	0101, 0102, 01031, 01032, 01033
	E3022		CACCAGGGAGCCTAC	0104

dization oven (Stuart Scientific, England) for 15 minutes at 42°C, in 10 ml of hybridization solution per 100 cm^2 of membrane (5x standard saline citrate [SSC], 1% blocking agent, 1% N-lauroylsarcosine, and 0.02% sodium dodecyl sulfate [SDS]). Hybridization was carried out at 42°C for 1 hour with γ-^{32}P-ATP labeled-SSOPs. Poshybridization washing was done as follows: 5xSSC at 42°C for 10 minutes and twice for 10 minutes at 50°C in the same solution. Hybridization signals were detected by exposing the blots DNA to a phosphor screen and visualized on Phopholmager using ImageQuaNT software (Molecular Dynamics, USA).

DNA sequencing

Sequencing was used to screen for additional polymorphism at other locations besides the one previously characterized and used to confirm the accuracy of PCR-SSOPs results. Exon 2 and exon 3 of HLA-E gene were amplified from genomic DNA samples of 10 healthy donors. For direct cycle sequencing, PCR products were purified by the QIAquick PCR Purification Kit (QIAGEN Inc., USA) to obtain clean double-standed DNA amplificates. Approximately 100 ng each of PCR products were sequenced with both directions of exon 2 and exon 3 primers as previously described[19,23]. The sequencing was undertaken using an ABI Prism 310 Genetic Analyzer by cycle sequencing chemistry with base-specific fluorescence-labeled dideoxynucleotide termination reagents, BigDye Terminator Ready Reaction Mix (Applied Biosystems, USA).

Statistical analysis

The number of HLA-E alleles was obtained using gene counting. The significant difference of the distribution of alleles between the two groups was tested by Chi-square (χ^2) method. Fisher' exact tests were applied if the expected frequency was less than 5. P-values of < 0.05 were considered to be significant.

RESULTS

HLA-E alleles of two hundred healthy individuals were investigated by the PCR-SSOP method. Sequence results from 10 healthy donors did not reveal any new polymorphism at the other locations besides the one previously characterized. The determination of each allele depends on the presence of specific nucleotide as shown in Table 1. For example, the HLA-E*0101 allele presents with polymorphism at the codon 83 (G/C) and the codon 107(A/G) both consisting in missence substitutions. A nonsynonymous conservative change from glycine to arginine at position 83(G/C) and a synonymous change of the codon 82(C/G) define the HLA-E*0102. The two alleles from the HLA-E*0103 lineage correspond to HLA-EG [A pattern of nucleotide substitution of HLA-E gene, which is Guanine (G)] at codon 107. A silent substitution (C/T) at codon 77 in exon 2 distinguished E*01032 from E*01031. The HLA-E*01033 allele corresponds to HLA-ET [A pattern of nucleotide substitution of HLA-E gene, which is Thymine (T)] at codon 150. The HLA-E*0104 allele is defined by a silent substitution at codon 2 (C/T) or a nonsynonymous change from arginine to glycine at amino acid position 157 (A/G). In this study, three alleles of HLA-E could be detected on the basis of these polymorphism. The HLA-E allelic frequencies (%) in three populations described in this study are shown in Table 3. The E*0101 is the most common allele in Thai and Thai-Chinese with allelic frequencies of 42.5 per cent and 38 per cent, respectively. The other HLA-E allele frequencies of Thai origin are 33 per cent and 24.5 per cent for E*01031 and E*01032, respectively. Among Thai-Chinese, the allele frequencies of HLA-E are 31 per cent for E*01031 and E*01032. Whereas the E*01031 was the predominant allele in Chinese origin with a frequency of 39 per cent, followed by E*0101 and E*01032 with 32 per cent and 29 per cent, respectively. No E*01033, E*0102 and E*0104 could be detected in all individuals.

When comparing the distribution of HLA-E alleles between each of study populations (Thai *vs* Chinese, Thai *vs* Thai-Chinese and Chinese *vs* Thai-Chinese), no significant difference could be found. In addition, the comparison of the HLA-E alleles distribution between the study populations and other populations, previously reported were analyzed[24-27] (Table 3). The analysis showed significant difference between each of the study populations (Thai, Chinese and Thai-Chinese) and Danish population ($\chi^2 = 15.64$, $p = 0.0004$; $\chi^2 = 24.58$, $p = 0.0000046$; $\chi^2 = 14.69$, $p = 0.00065$), respectively. In addition, when compared to an African population, only Chinese origin showed a significant difference with $\chi^2 = 7.61$ and $p = 0.022$. No significant difference of the distri-

Table 3. HLA-E allelic frequencies (%) in different populations.

HLA-E allele	Thai [a] (n = 200)	Chinese [b] (n = 100)	Thai-Chinese [c] (n = 100)	Danish[24] (n = 300)	Shanghai Chinese[26] (n = 402)	Japanese[27] (n = 100)	Indigenous African[25] (n = 216)
0101	42.5	32	38	56.67	42.29	32	50.93
0102	0	0	0	0	0	0	0
01031	33	39	31	9.67	24.88	39	29.63
01032	24.5	29	31	33.67	32.84	29	19.44
01033	0	0	0	0	0	0	0
0104	0	0	0	0	0	0	0

[a] compared with Danish $\chi^2 = 15.64$, $p = 0.0004$.
[b] compared with Danish $\chi^2 = 24.58$, $p = 0.0000046$.
[c] compared with Danish $\chi^2 = 14.69$, $p = 0.00065$.
[b] compared with Indigenous African $\chi^2 = 7.61$, $p = 0.022$.

bution of HLA-E alleles between the study populations and Shanghai Chinese or Japanese population could be detected.

DISCUSSION

In the present study, the authors observed the presence of 3 out of 6 previously characterized HLA-E alleles, HLA-E*0101, *01031 and *01032. This finding was similar to those reported in African-American, Japanese, Danish, Shanghai Chinese and indigenous African[24-27]. Although the HLA-E *0102 and 0104 were not detected, it was not surprising because several studies also reported the absence of these alleles[24-27]. HLA-E*0102 has been reported in a small sample of Spanish with a frequency of 10 per cent[19]. Whereas, HLA-E*0104 was initially reported at a frequency of 4.5 per cent in Japanese individuals. The fact that these two alleles were not found in any of the samples in the present study or other studies[24-27], suggest that the frequencies of these alleles are actually lower than previously reported or they may not exist. HLA-E*01033 was also not detectable in the present study. However, other studies did not analyze the distribution of this allele[19,24-27]. In the present study, the data of HLA-E allele frequencies reveal the limited polymorphism of HLA-E with some different patterns in the distribution of alleles in ethnically non-related populations.

However, a recent study of nucleotide variation of HLA-E in humans and macaques found evidence of selection acting on this gene. Regardless of which form of selection has influenced the patterning of alleles, their data suggest that HLA-E has not evolved neutrally and that functional differences between HLA-E alleles may exist[20]. In addition, increasing evidence suggests that HLA-E variation could also play a role in human health. For example, the expression of HLA-E may influence the success of transplantation. The frequency of graft *versus* host disease (GVHD) in HLA-matched donor transplants indicates that other polymorphic genetic factors must also be involved[28]. HLA-E is a prime candidate for such a genetic factor. One experiment also showed that two alleles differing at amino acid position 107, which is either a glycine (HLA-EG) or an arginine (HLA-ER) affect different function of natural killer (NK) cell. For example, HLA-EG allele presents the leader peptide from HLA-G or HLA-A2 leading to inhibit NK cell-mediated lysis. Whereas HLA-ER showed no inhibition in NK cell-mediated lysis[29]. The different HLA-E alleles seem to bind leader peptide and inhibit NK cell differently, suggesting the role HLA-E alleles in determining disease susceptibility or resistance. One recent study reported the association between the HLA-E alleles and susceptibility to type 1 diabetes mellitus[23]. Therefore, although with limited polymorphism, the analysis of HLA-E distribution in various patient groups might help further elucidate the role of HLA-E in disease susceptibility or resistance.

In summary, the authors examined HLA-E polymorphism in Thailand, which comprised Thai, Chinese and Thai-Chinese populations. These populations were found to contain low levels of allelic polymorphism similar to ethnic groups from Asian countries.

ACKNOWLEDGEMENTS

The authors wish to thank the staff of the National Blood Center for the recruitment of the material. This study was supported by the Ministry of University Affairs (MUA)-CU Thesis Grant for Graduate Students in Public Universities (2002), and the Molecular Biology Project, Faculty of Medicine, Chulalongkorn University.

(Received for publication on April 6, 2003)

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การศึกษาการกระจายของ HLA-E alleles ในประเทศไทย

อิงอร กิมกง, วทบ,*
*อภิวัฒน์ มุทิรางกูร, พบ, ปรด**, ณัฏฐิยา พิมทะโนทัย, พบ, ปรด****

การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาการกระจายของ HLA-E alleles ในประเทศไทย โดยใช้วิธี PCR-SSOP และ direct sequencing ในกลุ่มคนปกติ 200 คน ซึ่งประกอบด้วยเชื้อชาติไทย 100 คน เชื้อชาติจีน 50 คน และเชื้อชาติไทย-จีน 50 คน งานวิจัยครั้งนี้พบว่ามี HLA-E 3 ชนิด โดย HLA-E*0101 เป็นชนิดที่พบเป็นส่วนใหญ่ในคนเชื้อชาติไทย (42.5%) และไทย-จีน (38%) สำหรับชนิดอื่นที่พบในคนเชื้อชาติไทยคือ E*01031 (33%) และ E*01032 (24.5%) ในคนเชื้อชาติไทย-จีนพบชนิด E*01031 และ E*01032 เท่ากันคือ 31% นอกจากนี้ยังพบว่า E*01031 เป็นชนิดที่พบเป็นส่วนใหญ่ในคนเชื้อชาติจีน คือ 39% รองลงมาคือ E*0101 (32%) และ E*01032 (29%) การศึกษาครั้งนี้ไม่พบ HLA-E ชนิด E*01033, E*0102 และ E*0104 และเมื่อทำการเปรียบเทียบการกระจายของ HLA-E alleles ระหว่างแต่ละเชื้อชาติของการศึกษานี้ (ไทย *vs* จีน, ไทย *vs* ไทย-จีน และจีน *vs* ไทย-จีน) พบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ นอกจากนี้ยังได้ทำการเปรียบเทียบการกระจายของ HLA-E alleles ระหว่างกลุ่มประชากรที่ศึกษากับกลุ่มประชากรอื่นที่มาจากประเทศในทวีปเอเชีย พบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติเช่นเดียวกัน อย่างไรก็ตามเมื่อเปรียบเทียบระหว่างแต่ละเชื้อชาติของกลุ่มประชากรที่ศึกษา (ไทย, จีน และไทย-จีน) กับชาวเดนมาร์กพบว่ามีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (χ^2 = 15.64, p = 0.0004; χ^2 = 24.58, p = 0.0000046; χ^2 = 14.69, p = 0.00065 ตามลำดับ)

คำสำคัญ : เอ็ชแอลเอ-อี, อัลลีล, ปฏิกิริยาลูกโซ่โพลีเมอร์เรส-เอสเอสโอพี, การหาลำดับเบสของดีเอ็นเอ

อิงอร กิมกง, อภิวัฒน์ มุทิรางกูร, ณัฏฐิยา พิมทะโนทัย
จดหมายเหตุทางแพทย์ ฯ 2546; 86 (ฉบับพิเศษ 2): S230-S236

* สหสาขาวิชาจุลชีววิทยาทางการแพทย์, บัณฑิตวิทยาลัย,
** ภาควิชากายวิภาคศาสตร์,
*** ภาควิชาจุลชีววิทยา, คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพ ฯ 10330