Original Article

Frequencies of *HPA-1* to *HPA-11*, *HPA-13*, *-14*, *-15* and *HPA-17* in Thai blood donors

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Abstract:

Introduction: *Human platelet antigen (HPA) systems are involved in fetal-neonatal thrombocytopenia, platelet transfusion refractoriness, and post-transfusion purpura. The HPA genotyping is beneficial in the diagnosis and treatment.* ***Objective:*** *This retrospective study aimed to determine genotype frequencies of HPA-1 to HPA-11, HPA-13 to HPA-15 and HPA-17 in Thai blood donors.* ***Materials and Methods:*** *Totally, 10,510 donor samples were genotyped for HPA-1, -2, -4, 5, and HPA-6, and extended genotypes by real time-PCR. Consequently, 2,009 samples were genotyped for HPA-3, -7, -8, -9, -10, -11, -13, -14,-15 and HPA-17. The frequencies were compared with other populations previously reported.* ***Results****: Among blood donors, the frequencies of HPA-1a and HPA-1b were 0.981 and 0.019; HPA-2a and HPA-2b were 0.953 and 0.047; HPA-3a and HPA-3b were 0.564 and 0.436, respectively. The frequencies of HPA-4a and HPA-4b were 0.999 and 0.001; HPA-5a and HPA-5b were 0.967 and 0.033 and HPA-6a and HPA-6b were 0.985 and 0.015. For the HPA extended genotypes, the most common was homozygous aa, followed by heterozygous ab and homozygous bb was rare. The HPA-4b4b was not found while, only one donor with HPA-6b6b was observed. The prevalence rates of HPA-1 to HPA-6, and HPA-15 were similar to a related study in Thai blood donors and showed significantly different from other Asian populations previously reported.* ***Conclusion:*** *This study showed genotype frequencies of HPA-1 to HPA-6, and HPA-15, and extended genotypes in Thai blood donors. This data is useful to provide HPA-matched platelet donors for patients with HPA antibodies. In addition, the data file could provide appropriate panel cells not only to identify antibody specificity but also to increase transfusion safety.*

Keywords : ● *Human platelet antigen* ● *HPA* ● *Genotype frequencies* ● *Thai blood donors*

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Introduction

Human platelet antigen (HPA) system is of clinical importance especially in venous thrombosis, myocardial infarction, platelet transfusion refractoriness (PTR), post-transfusion purpura (PTP), drug-induced immune thrombocytopenia, fetal-neonatal alloimmune thrombocytopenia (FNAIT).[1-4] Currently, The Platelet Working Party of the International Society of Blood Transfusion (ISBT) had defined HPA into 29 systems i.e. HPA-1 to HPA-29w. Even though, the majority of antibodies found in patients with PTR, PTP and FNAIT were antibodies against human leukocyte antigen (HLA). However, some patients may be affected by HLA and /or HPA. Therefore, the patient antibody identification and preparation of compatible platelets for ABO and HLA or HPA are necessity.[5] HPA antibodies which cause clinical problems mainly are antibody to HPA-1 to HPA-5 and HPA-15. For Thailand, previous study by Atthapol Srisuddee, et al.[6] found that among 508 PTR and FNAIT cases which were sent to National Blood Centre (NBC), The Thai Red Cross Society for matched platelet requesting, majority of them were antibodies to HLA 84.26%, HLA with HPA 13.27% and to HPA 2.47%. For patients with HLA and / or HPA antibodies, genotyping for HLA and/or HPA may be needed in order to prepare HLA and/or HPA-matched platelets which are compatible with the patients.[6-8]

At present, many techniques for genotyping of HPA are available such as polymerase chain reaction with sequence-specific primer (PCR-SSP), multiplex PCR, real time PCR and high-throughput technology, e.g. Bead arrays.[7,9] Since 2005, The Special Laboratory, NBC applied PCR-SSP technique for *HPA-1* to *HPA-6* and *HPA-15* genotyping in 500 blood donor samples.[10] Later on in 2012, using multiplex PCR to type for *HPA-1* to *HPA-6* and *HPA*-15 in order to reduce steps of testing procedures and the cost. Nevertheless, the result showed no difference with previous report, i.e. *HPA-1b, -2b*, *-5b* and *-6b* frequencies were less common, while *HPA-1b1b* and *HPA-4b4b* were not found in both periods of study. Additionally, HPA-*7b* also was not found in Thai blood donors.[11] In 2015, there was a comparative study on genotypes HPA-*1* to *HPA-6* and *HPA-15* using real time PCR and multiplex PCR testing DNA samples from 500 blood donors. Among these, there were 300 cases of known genotypes and 200 of unknown genotypes. The result was 98.4% concordance. The real time PCR testing showed discrepancy for *HPA-5*, *HPA-6* and *HPA-15* genotypes. The results were confirmed using DNA sequencing.[12] However, there was limitation in using multiplex PCR for HPA genotyping. It is well documented that pre- and post-PCR analysis highly need personnel experience and time consuming technique. So it is not suitable for testing the large number of samples at the same time. Therefore, the Special Laboratory employed real time PCR technique for HPA genotyping for the patients and blood donors which enable us to test for more HPA genotypes leading to increase the chance to select HPA-matched and compatible platelets for the patients with antibodies. The aim of this study was to retrospective study for the data on genotype frequencies for *HPA-1* to *HPA-6* and *HPA-15* and genotype frequencies for *HPA-7* to *HPA-11*, *HPA-13*, *HPA-14* and *HPA-17* in Thai blood donors.

Materials and Methods

Study population

Retrospectively study on the genotyping of *HPA-1* to *HPA-6* and *HPA-15* in addition to *HPA-7* to *-11*, *-13*, *-14* and *HPA -17* in Thai blood donors at National Blood Centre, The Thai Red Cross Society from November 23, 2012 to September 30, 2019.

This study was approved by the research ethic committee of NBC, The Thai Red Cross Society. Approval number was 20/2019

Methods

Blood donor HPA data performed by real time PCR (Roche Diagnotics, Mannheim, Germany) at Special Laboratory, NBC were collated and analized. The procedure was to test DNA samples for genotyping using Light Cycler 480 system (Roche Diagnostics, Mannheim, Germany). The HPA reagent kit consisted of sequence

specific primers and specific probes. The procedures were performed strictly follow the manufacturer's instructions and recommendations which were as follows: a total of 10 μL of PCR reaction mixture per well by adding 5.7 μL PCR-grade water added to 0.5 μL Reagent Mix containing all primers and probes 1 μL 10× LightCyclerFastStart DNA Master HybProbe, 0.8 μL $MgCl_2$ (3.0 mM) and 2 μL DNA sample (concentration 50-100 ng/μL). Then the DNA quantity was increased by using real-time PCR model LightCycler 480 (Roche Diagnostics, Rotkreuz, Switzerland). The temperature and PCR conditions were set and initially first set 95°C for 10 min. For denaturation 95°C for 10 sec., annealing at 60°C for 10 sec., extension 72°C for15 sec. for 45 cycles. Then, melting curve analysis was performed at 95°C for 30 sec. and decreased to 40°C for 2 min. During increased the temperature to 75°C. The machine automatically analyzed the fluorescence reading every change of 1°C and expressed the result as melting curve of probe that specific to HPA gene by using melting curve analysis program of LightCycler 480 version 1.5.0.39. In case the result showed positive to a/a homozygous, only one melting temperature curve should be observed of that probes. If the result showed positive to b/b homozygous, a melting temperature should be observed at another temperature range. If the result showed positive to a/b heterozygous, two melting temperature will be observed at each temperature range. (Figure 1)

A) *HPA-1a1a*

B) *HPA-1a1b*

C) *HPA-1b1b*

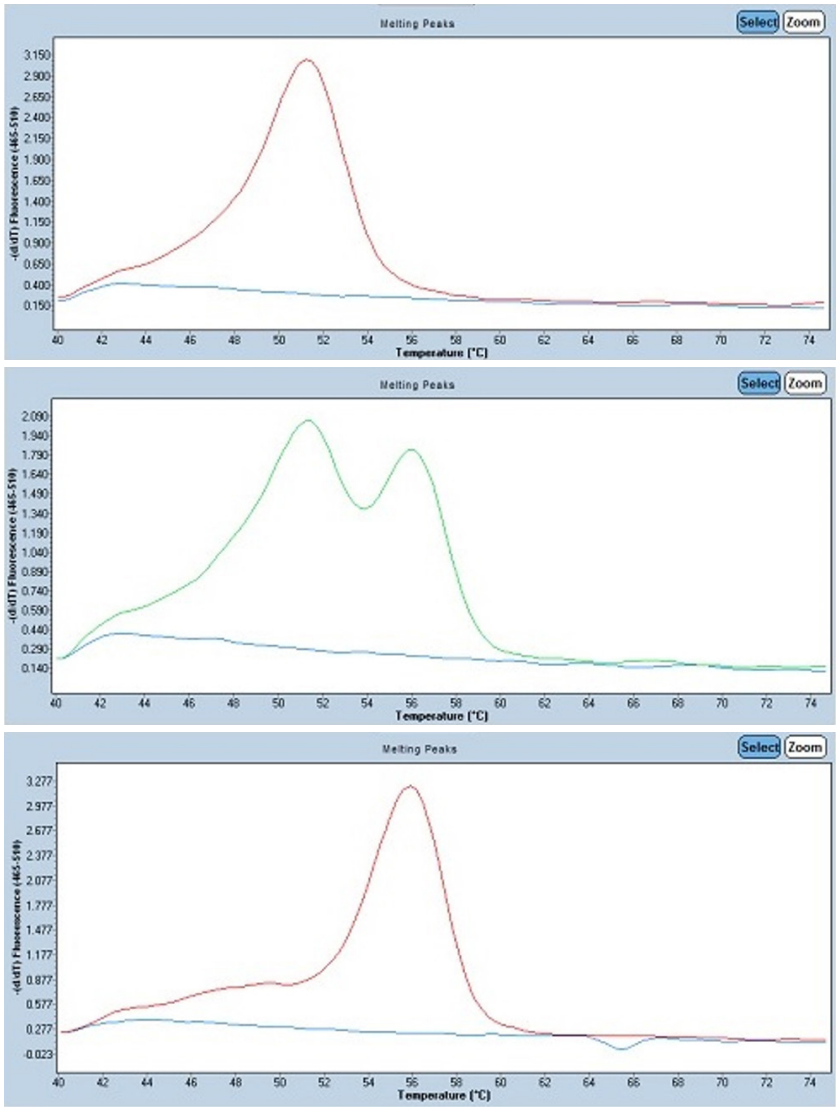

Figure 1 Melting curve analysis of *HPA-1a1a* (A), *HPA-1a1b* (B) and *HPA-1b1b* (C) using simple-probe real-time PCR technique

Data analysis

Genotype frequencies of each HPA system were expressed in number and percentage. The results of genotype and gene frequencies as compared to previous reports in other populations using Chi-square test and Fisher's exact test to determine the significant difference by SPSS software (version 23.0; SPSS Inc., Chicago, IL, USA) p-value < 0.05 indicates statistically significant difference.

Results

For the first period of study, from November 2012 to September 2014. A total of 2,009 DNA samples from blood donors were tested for genotypes HPA-1 to HPA-6 and HPA-15, HPA-7 to HPA-11, HPA-13, HPA-14 and HPA-17 by real time PCR. For *HPA-1b*, *-2b* and *-5b*, the rare genotypes among Thais, they were: *HPA-1b1b*, *-2b2b* and *-5b5b* were 1, 5 and 2 respectively. While *HPA-4b4b* and *HPA-6b6b* were not found, the genotype frequencies of 6 HPA system, i.e. *HPA-1a* and *HPA-1b* were 0.981 and 0.019, *HPA-2a* and *HPA-2b* were 0.953 and 0.047, *HPA-3a* and *HPA-3b* were 0.564 and 0.436, *HPA-4a and HPA-4b* were 0.999 and 0.001, *HPA-5a* and *HPA-5b* were 0.967 and 0.033, *HPA-6a* and *HPA-6b* were 0.985 and 0.015 and *HPA-15a* and *HPA-15b* were 0.530 and 0.470, respectively, (Table 1). After testing other systems of HPA, it was revealed that *HPA-7b*, *-9b*, *-11b* and *HPA-13b* were not found in this population. So genotype frequencies of *HPA-7a*, *-9a*, *-11a* and *-13a* were equal to 1.000 (Table 1), while *HPA-8a8b*, *-10a10b*, *-14a14b* and *-17a17b* were 2, 1, 2 and 1, respectively, which genotype frequencies of *HPA-8a* and *HPA-8b* were 0.999 and 0.001, *HPA-10a* and *HPA-10b* were 0.999 and 0.001, *HPA-14a* and *HPA-14b* were 0.999 and 0.001, *HPA-17a* and *HPA-17b* were 0.999 and 0.001, respectively.

According to the low incidence of some clinically significant HPA genotypes, they were rarely found in the previous 2,009 blood donor samples, As NBC needs to prepare standard screening cells that suitable for the detection of platelet antibody frequently found in Thai patients. Then during October 2014 to September 2019, a total of 8,501 donor blood samples were tested for *HPA-1*, *-2*, *-4*, *-5* and HPA *-6* by real time PCR. Consequently, *HPA-1b1b*, *-2b2b*, *-5b5b*, and *-6b6b* were detected 4, 22, 10 and 1, respectively.

The genotype frequencies of *HPA-1* to *HPA-6* and *HPA-15* in 2,009 blood donors as compared to central Thai blood donors[10] showed no statistically significant difference. However, the statistically significant difference for *HPA-1* only was observed when compared with North-eastern Thai blood donors[13] (p < 0.05). No statistically significant difference observed when compared with previously reports in other Asian populations.[13-19] For *HPA-1* genotype frequency, no statistically significant difference observed when compared with Vietnamese and Korean populations (p > 0.05) but there was statistically significant difference when compared with populations of Malay-Malay, Japan, Han Chinese and Taiwan (p < 0.05). While *HPA-2* genotype frequency was significantly different as compared with Korean, Japanese and Han Chinese (p < 0.05). And for *HPA-3* genotype frequency, statistically significant difference was observed when compared with Malay-Malay, Vietnamese, Japanese and Han Chinese (p < 0.05). For *HPA-4* genotype frequency, statistically significant difference was observed when compared with Malay-Malay, Korean, Japanese and Han Chinese (p < 0.05). While *HPA-5* genotype frequency showed statistically significant difference with Malay-Malay and Han Chinese (p < 0.05). In addition, *HPA-6* genotype frequency showed statistically significant difference with Taiwan. While *HPA-15* genotype frequency showed no statistically significant difference with all populations (p > 0.05) (Table 2).

Discussion

To study for *HPA* genotype frequency especially those with clinically significance, i.e. HPA-1 to HPA-6 and HPA-15, besides the selection of HPA-matched for the patients with platelet antibodies, it is also for platelet standard screening cells production. To study the *HPA* gene and genotype frequencies both HPA-1 to HPA-6 and HPA-15 including other systems which

Table 1 Genotype and gene frequencies of *HPA-1 to HPA-11, HPA-13, -14, -15 and HPA-17* in Thai blood donors

HPA	Genotype (%)			Gene frequencies	
	aa	***ab***	***bb***		
HPA-1	10,122	383	5	*HPA-1a*	0.981
	(96.31)	(3.64)	(0.05)	*HPA-1b*	0.019
HPA-2	9,548	935	27	*HPA-2a*	0.953
	(90.85)	(8.9)	(0.26)	*HPA-2b*	0.047
HPA-3	651	965	393	*HPA-3a*	0.564
	(32.4)	(48.03)	(19.56)	*HPA-3b*	0.436
HPA-4	10,489	21	0	*HPA-4a*	0.999
	(99.8)	(0.2)	(0)	*HPA-4b*	0.001
HPA-5	9,821	677	12	*HPA-5a*	0.967
	(93.44)	(6.44)	(0.11)	*HPA-5b*	0.033
HPA-6	10,186	323	1	*HPA-6a*	0.985
	(96.92)	(3.07)	(0.01)	*HPA-6b*	0.015
HPA-7	2,009	0	0	*HPA-7a*	1.000
	(100)	(0)	(0)	*HPA-7b*	0.000
HPA-8	2,007	2	0	*HPA-8a*	0.999
	(99.9)	(0.1)	(0)	*HPA-8b*	0.001
HPA-9	2,009	0	0	*HPA-9a*	1.000
	(100)	(0)	(0)	*HPA-9b*	0.000
HPA-10	2,008	1	0	*HPA-10a*	0.999
	(99.95)	(0.05)	(0)	*HPA-10b*	0.001
HPA-11	2,009	0	0	*HPA-11a*	1.000
	(100)	(0)	(0)	*HPA-11b*	0.000
HPA-13	2,009	0	0	*HPA-13a*	1.000
	(100)	(0)	(0)	*HPA-13b*	0.000
HPA-14	2,007	2	0	*HPA-14a*	0.999
	(99.9)	(0.1)	(0)	*HPA-14b*	0.001
HPA-15	542	1047	420	*HPA-15a*	0.530
	(26.98)	(52.12)	(20.91)	*HPA-15b*	0.470
HPA-17	2,008	1	0	*HPA-17a*	0.999
	(99.95)	(0.05)	(0)	*HPA-17b*	0.001

n of each HPA-1, -2, -4, -5, -6 is 10,510 donors; n of each HPA-3, -7, -8, -9, -10, -11, -13, -14, -15, -17 is 2,009 donors

Table 2 Gene frequencies of *HPA-1* to *-6* and *HPA-15* in Thai blood donors and Asian populations

Population	N	HPA												
		1a	*1b*	*2a*	*2b*	*3a*	*3b*	*4a*	*4b*	*5a*	*5b*	*6a*	*6b*	*15a*	*15b*
Thai (This study)	10,510	0.981	0.019	0.953	0.047	0.564*	0.436*	0.999	0.001	0.967	0.033	0.985	0.015	0.530*	0.470*
Central Thai[10]	500	0.985	0.015	0.952	0.048	0.560	0.440	0.100	0.000	0.968	0.032	0.986	0.014	0.509	0.491
Northeastern Thai[13]	300	0.972[b]	0.028[b]	0.938	0.062	0.533	0.467	1.000	0.000	0.963	0.037	0.985	0.015	0.495	0.505
Malay-Malay[14]	200	0.975[a]	0.025[a]	0.963	0.037	0.503[a]	0.497[a]	0.995[a]	0.005[a]	0.950[a]	0.050[a]	0.992	0.008	0.515	0.485
Vietnamese[15]	107	0.986	0.014	0.953	0.047	0.486[a]	0.514[a]	1.000	0.000	0.972	0.028	0.980	0.014	0.477	0.523
Korean[16]	200	0.988	0.012	0.923[a]	0.077[a]	0.555	0.445	0.990[b]	0.010[b]	0.978	0.022	NA	NA	NA	NA
Japanese[17]	331	0.998[a]	0.002[a]	0.900[b]	0.100[b]	0.718[b]	0.282[b]	0.989[b]	0.011[b]	0.973	0.027	NA	NA	NA	NA
Han Chinese[18]	1,000	0.994[a]	0.006[a]	0.952[b]	0.049[b]	0.595[a]	0.406[a]	0.996[b]	0.005[b]	0.986[b]	0.014[b]	0.986	0.014	0.532	0.468
Taiwanese[19]	566	0.997[b]	0.003[b]	0.960	0.040	0.575	0.425	0.998	0.002	0.985	0.015	0.963[a]	0.037[a]	0.538	0.462

NA = not applicable; [a]$p < 0.05$; [b]$p < 0.01$; *n = 2009

cause PTR, PTP and FNAIT will be very useful to predict the risk of platelet-specific alloimmunization of each population. Moreover, it is to increase the ability in providing compatible platelets for the patients.[20,21]

The result of HPA-*1* to *HPA-6* and HPA-*15* genotype frequencies in 2,009 blood donors showed no statistically significant difference when compared with HPA genotype distribution in the study of Pawinee Kupatawintu et al.[10] ($p > 0.05$). For *HPA-1b1b*, *HPA-2b2b* and *HPA-5b5b* which could not found in previous reports were observed after increasing in number of subjects. However, even increase the number of subjects, the rare genotypes as *HPA-4b4b* and *HPA-6b6b* were not found. In this study, *HPA-7*, *-8*, *-9*, *-10*, *-11*, *-13*, *-14*, and *-17* genotypes had been examined. It was found that majority of them were *homozygous aa* while *heterozygous ab* genotypes were lessly found. The *homozygous bb,* i.e. *HPA-7b*, *-9b*, *-11b* and *-13b* were not found which was similar to the study of Tomoya Hayashi et al. whose report indicated that no HPA-*7b*, *-8b*, *-9b*, *-10b*, *-11b*, *-13b*, *-14b* and *-17b*[22] genotypes detected among 2,170 Japanese blood donors. Then the patients in all population studied have rarely chance to produce antibodies to HPA-7b, -8b, -9b, -10b, -11b, -13b, -14b and -17b.

One subject with *HPA-6b6b* was found in additional tested among 8,501 blood donors, but no *HPA-4b4b* was observed. When more number of subjects were tested, *HPA-4a4b* was found indicating that HPA-*4b4b* was rare genotypes in Thai population. The patients with *HPA-4a4a* genotype may develop anti-HPA-4b after receiving HPA-*4a4b* genotype platelets. This antibody had been reported as the cause of NAIT in new born in Japanese and Caucasians.[23,24] On the other hand, *HPA-6b6b* and *HPA-6a6b* were found increased in number in this study indicating that anti-HPA-6b and anti-HLA may be found among Thai population.Atthapol Srisuddee et.al. found anti-HPA-6b and anti-HLA in a patient with thrombocytopenia.[6] For *HPA-1b1b* with 0.05% frequency indicating that patients with anti-HPA-1a causing thrombocytopenia, PTR, PTP and FNAIT may be found in Thai

population but lesser than Caucasians.[4,23,25-28] For *HPA-2b2b* and *HPA-5b5b* with 0.26% and 0.12% frequencies, respectively, indicating the possibility for the patients to produce anti-HPA-2a and anti-HPA-5a which can be the cause of PTP and FNAIT[28-30]

There were no statistically significant difference when compared *HPA-1* to *HPA-6* and *HPA-15* in Thai blood donors in this study and previously reported in central Thai blood donors[10] but they were significant difference only for *HPA-1* with north-eastern Thai blood donors.[13] When comparing *HPA-1* to *HPA-6* and *HPA-15* genotypes of Thai blood donors with other Asian populations previously reported in Malay-Malay, Vietnamese, Japanese, Korean, Chinese[14-19] and found that genotype of *HPA-15* was not significantly different from other studies in Thai blood donors.[10,19]

Conclusion

This study reported genotype frequencies of *HPA-1* to *HPA-11, -13, -14, -15* and *HPA-17* in Thai blood donors. This information can be used for providing HPA-matched platelets for the patients who possess platelet antibody, yet can be used to prepare suitable standard cells for platelet antibody identification. This will promote safe platelet transfusion for the patients.

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