HLA Gene Frequencies of Northern Thais

LADDA FONGSATIKUL, M.Sc.*, NIWES NANTACHIT, M.D.**,
NUONCHUEN KAMTORN, B.Sc.*, NIPAPAN LEETRAKOOL, B.Sc.*

Abstract

We investigated the distribution of HLA-A and B locus, gene frequency (GF), antigen frequency (AF), haplotype frequency (HF) and non detectable antigens in Northern Thais. Of 289 native northern Thai people residing in Chiang Mai province for many generations were tested using lymphocytotoxicity test and 146 unrelated subjects were selected for analysis. The common alleles were A2, A11 and A24 for A locus with GF of 36.4%, 35.4% and 15.6%, respectively and B46, B40 and B13 for B locus with GF of 21.1%, 15.7% and 8.6%, respectively. The frequent linkage disequilibrium haplotypes were A2,B46; A33,B17 with HF of 15.9%; 5.0% and LD of 8.3%; 4.6%, respectively ($p<0.0001$). The undetectable antigens (blanks) occurred with GF= 11.64% at A locus and GF=4.92% at B locus. Comparing the GFs to other Thai ethnic groups, showed that the Northern Thais shared several alleles such as A2, A11, B46, and B62 in common with Dai Lue (Thai-speaking people who lived in the southern part of China), ($p>0.05$), more than Thais, Thai/Chinese or present-day Thais ($p<0.001$). Especially, HLA-B46 with the GF of 21.1% is considered to be a very typical antigen for Southern Mongoloids. These similarities will support the root of migration and origin of Northern Thais.

HLA has been known as a great important part in organ transplantation, paternal serology, disease susceptibility throughout population genetics. The analysis of HLA class I allele frequencies will provide important background information relevant to the origin of ethnic Thais which has been an interesting subject for study in archaeology, anthropology and also in medical fields.

During the period of the fourteenth and nineteenth centuries[1], there were several massive mass migrations of Chinese to Thailand. Intermarriage between Thais and Chinese has been widespread resulting in a nearly completed admixture of the two populations. Thus, nowadays Thais can not be defined as a homologous Thais. "Dai Lue" is an ethnic Thai-speaking minority who lived in

* Blood Bank Section, Chiang Mai University,
** Department of Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.

Southern China and believed to be the original Thai people. Northern Thais are also ethnic Thais considered to be evidence of migration because they have shared some linguistic similarities, cultural styles, architecture, religion and agricultural practices with the Dai Lue. This leads to tracing the history of the people, believed to be their ancestors.

This study was carried out to investigate the distribution of HLA-A and -B locus, gene frequency, haplotype frequency, and non detectable antigen in Northern Thais (NT) which may support the origin of Thai people.

MATERIAL AND METHOD

A total of 289 native NT included 143 related and 146 unrelated were studied for HLA-A, B by microlymphocytotoxicity test(2). These people have resided in Chiang Mai province for many generations and never intermarried with migrant Chinese. The HLA-A and B serotyping trays, prepared by the Department of Transfusion Medicine,

Table 1. Antigen frequencies (AF) and gene frequencies (GF) of HLA-A in Northern Thais (N=146).

Specificity	Number	AF%	GF%
A1	1	0.68	0.34
A2	87	59.59	36.43
A3	1	0.68	0.34
A9			
A24	42	28.77	15.60
A10			
A26	4	2.74	1.38
A11			
A11.1	57	39.04	21.92
A11.2	13	8.90	4.55
A11*	25	17.12	8.96
A19			
A29	1	0.68	0.34
A30	2	1.37	0.69
A31	5	3.42	1.72
A33	21	14.38	7.47
A74	1	0.68	0.34
A blank			11.64

* = Subtype not available

Table 2. Antigen frequencies (AF) and gene frequencies (GF) of HLA-B in Northern Thais (N=146).

Specificity	Number	AF%	GF%
B5			
B51	14	9.59	4.92
B52	4	2.74	1.38
B5*	1	0.68	0.34
B7	5	3.42	1.72
B12 (B44)	8	5.48	2.78
B13	24	16.44	8.59
B14 (B64)	1	0.68	0.34
B15			
B62	6	4.11	2.08
B75	13	8.90	4.55
B76	3	2.05	1.03
B16			
B38	11	7.53	3.84
B39	8	5.48	2.78
B17			
B58	13	8.90	4.55
B17*	2	1.37	0.69
B18	4	2.74	1.38
B22			
B54	1	0.68	0.34
B55	4	2.74	1.38
B56	1	0.68	0.34
B22*	2	1.37	0.69
B27	17	11.64	6.00
B35	11	7.53	3.84
B40			
B60	30	20.55	10.87
B61	4	2.74	1.38
B40*	10	6.85	3.49
B46	55	37.67	21.05
B48	7	4.79	2.42
B blank			4.92
Bw4	82	56.16	33.79
Bw6	123	84.25	60.31

* = Subtype not available

Table 3. HLA-A,-B haplotype, haplotype frequency (HF) and linkage disequilibrium (LD) in Northern Thais (N=146).

Haplotype		HF(%)	LD(%)	X^2	P
A	B				
2	46	15.9	8.3	18.11	<0.0001
33	17	5.0	4.6	84.62	<0.0001

Faculty of Medicine, Mahidol University and Terasaki typing trays, were both used for testing.

Of the total 289 native NT, 146 proved to be unrelated and were used for calculation of gene frequency (GF) by GF (%) = $1-\sqrt{1-f} \times 100$, where f is the antigen frequency of the corresponding antigen[3]. Antigen frequencies (AF) were calculated by AF (%) = (sum of the given antigen/N) x 100, where n is the total tested number[4]. Haplotype frequencies were calculated by $(F_1 \times F_2) + \Delta$, where F_1 = GF of A-locus, F_2 = GF of B-locus, Δ = linkage disequilibrium of two linked genes. The Δ-value and Chi-square were calculated by formula[3]; $\Delta = \sqrt{d/n} - \sqrt{(b+d)(c+d)/N^2}$ and $X^2 = N(ad-bc)^2/(a+b)(a+c)(c+d)(b+d)$. The HLA-A,-B GFs were compared with other ethnic Thais previously reported by using Chi-Square test for heterogenicity, with Yates correction[5].

RESULTS

The antigen frequencies (AF) and gene frequencies (GF) of HLA-A and -B of 146 Northern Thais are shown in Table 1 and 2. The three most common HLA-A serotypes were A2, A11 and A24 with GF of 36.43%, 35.43% and 15.60% respectively, while the lowest ones were, A1 and A3 with GFs of 0.4%. The three most common HLA-B serotypes were B46, B40 and B13 with GF of 21.05%, 15.74% and 8.59%, respectively. The undetectable antigens (blanks) occurred with GF of 11.46% at A-locus and GF of 4.92% at B locus. Bw4 and Bw6 associated B-locus antigens frequencies were found to be 56.16% and 84.25%, respectively.

Table 3 shows the HLA haplotypes, haplotype frequencies (HF) and linkage disequilibrium (LD) found in Northern Thais. Two most common HLA haplotypes were HLA-A2,B46 and A33,B17 with HF = 15.9% and 5.0% and LD = 8.3% and 4.6%, respectively ($p<0.0001$).

The comparison of HLA-A and B gene frequencies (GFs) between Northern Thai, Dai Lue[1], Thais[1],Thai/Chinese[1] and present-day Thais[6] are shown in Table 4. Only the most prevalent serotypes in those Thai groups were illustrated, which were A2, A11, A24, A33, B44, B46, B58 and B62. There were no significant differences in GFs for HLA-A2, A11, B46 and B62 between Northern Thais and Dai Lue ($X^2 = 1.29$, $p>0.05$), but it revealed significant differences between Northern Thais and Thais, Thai/Chinese or present-day Thais ($p<0.0001$). These differences were also found in the GFs of HLA-A24, A33, B44 and B58 ($p<0.001$).

DISCUSSION

It was seen quite clearly that the HLA-A2, A11, B46 and B40 were commonly found in Northern Thais. The distribution of both A and B locus are similar to those previous reports in Thais[7-9], Northern Thais[10] and present-day Thais[6]. The HLA-A10 found in this study was classified as A26. Other splits of A10 were totally lacking in Northern Thais, which is similar to those previous reports of this rare antigen in the Thai population[7]. For HLA-A11 antigen, about 17.12% could not be identified as A11.1, A11.2 or other subtypes. Therefore, further studies of higher resolution of HLA-A11 subtyping may help solve these problems.

The linkage disequilibrium, the alleles of HLA linked loci in Northern Thais, were found positive between the A2 and B46, A33 and B17 linked genes. These haplotypes, A2,B46 and A33, B17 occurred more often than expected by chance alone based on gene frequency with LD of 8.3% and 4.6% with $p<0.0001$. No significant linkage disequilibrium was found in other haplotypes, $p>0.05$.

Table 4. Comparison of HLA-A and -B gene frequencies (GF%) in Northern Thais with other Thai ethnics.

HLA Specificity	NT n=146	DL[1] n=105	Thais[1] n=137	Thai/Chinese[1] n=71	PDT[6] n=140
A2	36.4	36.7	18.9	25.0	19.6
A11	35.4	37.2	24.5	28.6	28.9
A24	15.6	10.0	19.4	16.7	18.1
A33	7.5	9.5	18.0	18.7	14.6
B44	2.8	1.4	8.4	2.8	7.9
B46	21.1	21.3	8.8	7.7	9.4
B58	4.6	1.4	4.1	15.5	4.6
B62	2.1	2.4	7.2	7.0	8.2

NT = Northern Thais, DL = Dai Lue, PDT = Present-day Thais

NT vs DL : X^2 = 1.29, p>0.05

(1) Data from Chandanayingyong et al, 1992 (Ref. 1)

(10) Data from Chandanayingyong et al, 1997 (Ref. 6)

The HLA-A, -B gene frequencies of Northern Thais and Dai Lue have revealed interesting similarities. Compared to other Thai ethnic groups previously reported[1,6], it indicated that the Northern Thais shared several alleles such as A2, A11, B46 and B62 in common with Dai Lue. Especially, B46 antigens with the GF of 21.1% in Northern Thais and 21.3% in Dai Lue were considered to be very typical antigens of Southern Mongoloids. This would suggest that these two ethnic Thai groups may come from the same origin. This finding will support the migration origin of Northern Thais. Moreover, this study will also provide important background information relevant to transplantation and disease association in Northern Thailand.

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REFERENCES

1. Chandanayingyong D, Kunmarti S, Udee S, et al. HLA in Thais, Thai-Chinese, Vietnamese, Javanese and Timorese. In Tsuji K, Aizawa M, Sasazuki T (eds) : HLA 1991. New York, Oxford University Press, 1992; 681-3.
2. Terasaki PI, Bernoco D, Park MS, Ozturk G, Iwaki Y. Microdroplet Testing for HLA-A, -B, -C and -D antigens. Am J Clin Pathol 1978; 69: 20.
3. Svejgaard A, Hauge M, Jersild C, et al. The HLA system, an introductory survey. In Beckman L, Hauge M (eds) : Monographs in Human Genetics. Vol.7 Basel, New York, Karger, 1979.
4. Chandanayingyong D, Stephens HAF, Fan L, et al. HLA-DPB1 polymorphism in the Thais of Southeast Asia. Hum Immunol 1994; 40: 20-4.
5. Morel PA. Data Analyses and Tests for Statistical Significance. Ellisor SS. Statistics for Blood Bankers. AABB, 1983; 123-6.
6. Chandanayingyong D, Stephens HAF, Klaythong K, et al. HLA-A, -B, -DRB1, -DQA1 and -DQB1 polymorphism in Thais. Hum Immunol 1997; 53: 174-82.
7. Chiewsilp P, Chanarat P. The HL-A system in Thais. Vox Sang 1976; 30: 74-80.

8. Chandanayingyong D, Chiewslip P. HLA antigens in Thais. In Simons MJ, Tait BD (eds) : Proceedings of the second Asia and Oceania Histocompatibility Workshop Conference, Victoria, Immunopublishing, 1983.
9. Chiewsilp P, Scott RM, Bhamarapravati N. Histocompatibility antigens and dengue hemorrhagic fever. Am J Trop Med Hyg 1981; 30: 1100-5.
10. Greiner J, Schleiermacher E, Lenhard V, Kulapongs P, Vogel F. HLA antigen, gene, and haplotype frequencies in Thailand. Hum Genet 1978; 41: 73-87.

ศึกษาความถี่ของยีน HLA ในคนไทยภาคเหนือ

ลัดดา ฟองสถิตย์กุล, วท.ม., นิเวศน์ นันทจิต, พ.บ.**, นวลชื่น คำทอน, วท.บ.*, นิภาพรรณ ลี้ตระกูล, วท.บ.**

ได้ทำการตรวจ HLA-typing ของ A และ B locus ในคนพื้นเมืองของจังหวัดเชียงใหม่ จำนวน 289 ราย แบ่งเป็น related sample 143 ราย และ unrelated sample 146 ราย คนพื้นเมืองเหล่านี้มีบรรพบุรุษที่อาศัยอยู่ในภาคเหนือมาหลายชั่วอายุ โดยการแต่งงานระหว่างคนพื้นเมืองด้วยกันเอง ไม่ได้ผสมกับคนไทยภาคกลาง, คนจีน หรืออื่นๆ การทดสอบใช้วิธี microlymphocytotoxicity test ผลการทดลองพบอุบัติการ gene frequency (GF) ของ HLA-A และ B Antigen ใน unrelated sample ดังนี้ A2(36.4%), A11(35.4%), A24(15.6%), B46(21.1%), B40(15.7%), B13(8.6%). การศึกษา linkage disequilibrium (LD) ของ HLA-haplotypes พบว่ามีการจับคู่ของ A และ B locus ในประชากรภาคเหนือสูงกว่าค่าที่น่าจะเป็นซึ่งคำนวนได้จากความถี่ของยีน Haplotypes ดังกล่าวได้แก่ A2,B46 และ A33,B17 ซึ่งพบ HF เท่ากับ 15.9%, และ 5.0% โดยมีค่า LD เท่ากับ 8.3% และ 4.6% ตามลำดับ ($p < 0.0001$) ส่วนแอนติเจนที่ตรวจไม่ได้ (blanks) พบที่ locus A GF=11.64% และ locus B GF=4.92%.

การศึกษาเปรียบเทียบ gene frequency ระหว่างประชากรไทยกลุ่มต่างๆ ที่เคยมีผู้รายงานไว้พบ HLA-A2, A11, B46, และ B62 ของคนไทยภาคเหนือใกล้เคียงกับคนไทยลื้อจากสิบสองปันนา อย่างมีนัยสำคัญ $p>0.05$ โดยเฉพาะอย่างยิ่ง B46 antigen ซึ่งเป็น antigen ที่พบได้สูงมากในคน Mongoloid ที่อยู่ทางภาคใต้ ในคนไทยภาคเหนือพบ B46 ถึง 21.1% ซึ่งต่างกับประชากรกลุ่มอื่นๆ ยกเว้นไทยลื้อ อย่างไรก็ตามข้อมูลดังกล่าวข้างต้น อาจนำมาใช้สนับสนุนหลักฐานด้านโบราณคดี และมนุษยวิทยาเกี่ยวกับแหล่งกำเนิดของคนไทย นอกจากนี้ยังสามารถนำไปเป็นบรรทัดฐานในการตรวจหา HLA-antigen ในคนภาคเหนือ เพื่อใช้ประโยชน์ในการเปลี่ยนไตหรือไขกระดูก รวมทั้งการศึกษาทางด้านภูมิต้านทานที่เกี่ยวกับการกำเนิดโรคต่าง ๆ เป็นต้น

* งานธนาคารเลือด,
** ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่, เชียงใหม่ 50200