ARTIKEL PENELITIAN

Nasopharyngeal Carcinoma (NPC) Related Human Leukocyte Antigen (HLA) Haplotype Sharing among Southern East Asian Population

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Abstract

The human leukocyte antigens (HLAs) play important roles in the immune systems to response to various pathogens and disease among individuals. The aim of this study was analyze the HLA allele and haplotype frequencies of Southern East Asian population that show high incidence of nasopharyngeal carcinoma (NPC) to evaluate the shared HLA haplotype contribution to NPC susceptibility among the population and analyses the genetic affinities between the population. We collect information of HLA haplotype from our previous study, other published paper, and HLA database in 19 population during 2005 to 2015. Haplotype frequencies were estimated using the maximum likelihood method based on an expectation maximization algorithm with ARLEQUIN v.2.0 software. We also calculated the genetic distance among 19 Southern East Asians based on HLA allele frequency using modified Cavalli-Sforza (DA) distance method. Then, a phylogenetic tree was constructed using DISPAN software and principal component analysis (PCA) was performed using XLSTAT-PRO software. A33-B58-DR3 haplotype, tightly linked to NPC, was commonly observed in all populations, supporting the high incidence of NPC in the populations. In addition, A2-B46 haplotype also associated with NPC, was also commonly found in several population that may also have a role in the disease development. The conclusion is the HLA haplotype sharing has an important role than the HLA allele sharing. The A33-B58-DR3 haplotype and A2-B46-DR9 haplotype in this study could be related to NPC in the Southern East Asian populations. The observed haplotype needs to be tested in the real patients to confirm the assumption.

Key words: HLA allele, HLA haplotype, nasopharyngeal carcinoma, Southern East Asian

Penyebaran Haplotipe *Human Leukocyte Antigen* (HLA) Terkait *Nasopharyngeal Carcinoma* (NPC) pada Populasi Asia Timur Bagian Selatan

Abstrak

Human leukocyte antigens (HLAs) berperan penting dalam sistem imun untuk merespons berbagai patogen dan penyakit di antara individu yang berbeda. Tujuan penelitian ini menganalisis frekuensi alel dan haplotipe HLA populasi *Southern East Asia* yang menunjukkan insidensi yang tinggi terhadap *nasopharyngeal carcinoma* (NPC) untuk mengevaluasi kerentanan NPC bagi individu. Informasi haplotipe HLA dikumpulkan dari studi sebelumnya, publikasi jurnal internasional, dan *database* HLA pada 19 populasi dalam periode tahun 2005–2015. Frekuensi haplotipe dihitung menggunakan metode *maximum likelihood* berdasarkan *expectation maximization algorithm* menggunakan piranti lunak ARLEQUIN v.2.0. Jarak genetik di antara 19 populasi *Southern East Asians* dihitung menggunakan metode *modified Cavalli-Sforza* (DA) *distance*. Kemudian, pohon filogenetik dikonstruksi dengan metode *neighbor-joining* (NJ) menggunakan piranti lunak DISPAN. *Principal component analysis* (PCA) dilakukan menggunakan piranti lunak XLSTAT-PRO. Haplotipe A33-B58-DR3 terkait erat dengan NPC yang biasa terlihat di semua populasi mendukung tingginya insidensi penyakit dalam populasi. Selain itu, haplotipe A2-B46 juga terkait dengan NPC yang juga ditemukan pada beberapa populasi sehingga kemungkinan memiliki peran dalam perkembangan penyakit. Pada kasus NPC, haplotipe HLA lebih berperan dibanding dengan alel HLA. Haplotipe A33-B58-DR3 dan haplotipe A2-B46-DR9 yang ditemukan terkait dengan NPC pada populasi *Southern East Asia*. Haplotipe yang diamati tersebut perlu diuji pada pasien nyata untuk mengonfirmasi simpulan.

Kata kunci: HLA alel, HLA haplotipe, *nasopharyngeal carcinoma*, *Southern East Asia*

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Introduction

The human leukocyte antigens (HLAs) play central roles as antigen-presenting molecules in the immune systems and result in the differences in the response to various pathogens and diseases among individuals such as: bacterial disease (tuberculosis, SARS, Avian influenza, etc.) and viral disease {HIV, nasopharyngeal carcinoma (NPC)}. The highly polymorphic HLA molecules also lead to a diversity of allele and haplotype frequencies among various human populations. In general, populations sharing similar patterns of HLA allele distribution are likely to have a relatively close genetic relationship and share the disease distribution pattern.[1]

East Asian population is consistently reported to have two population groups division that are Southern and Northern groups used for studies using various genetic markers such as Y chromosome,[2,3] mtDNA,[4] and HLA.[5–7] The genetic studies of human diversity in East Asian and the migration routes of ancestral populations also have been investigated, emphasizing the history of East Asian and the North-South differentiation in Chinese population.[3,8]

Southern China and Southeast Asia have been reported to be endemic regions of NPC, one of the most common cancers in Asians but it is rare in Caucasians.[9–12] The highest prevalence was found in The Guandong Province in South China, with approximately 20 to 40 cases per 100,000. The previous study also showed the highest incidence (54.7/100,000) were in Cantonese “Boat People”. Southeast Asia region showed the intermediate incidence rates of NPC, including Singapore (15/100,000), Malaysia (9.7/100,000), Vietnam (7.5/100,000), Taiwan (7/100,000), and the Philippines (6.4/100,000). In Indonesia, NPC incidences estimated at 6.2/100,000 or about 12,000 new cases per year.[13]

One of the strongest and most consistent genetic marker to be associated with the disease risk is HLA as firstly reported by Simons et al. and in recent GWAS study.[14] HLA-A*02(A*02:07), A*33, B*46, and B*58 showed an association with susceptibility to this disease in Chinese of Singapore, Guangdong, and Taiwan.[15,16] NPC also has been strictly associated with certain HLA haplotypes: A*02:07-B*46:01 ($p=0.01$) and A*33:03-B*58:01 ($p=0.0003$) haplotypes.[17] The extended haplotype HLA-A*33:03-B*58:01/2-DRB1*03:01-DQB1*02:01/2-DPB1*04:01, was also reported to be significantly associated with increased risk for NPC (OR=2.6, 95% CI=1.1 to 6.4).[18] A2-B46-DR9 haplotype was significantly associated with autoimmune thyroid dysfunction in Chinese ($p<0.001$) that may also has a role in NPC susceptibility.[19]

So far there is no study reporting the shared HLA allele and haplotype among population with high-incidence of NPC. Therefore, study of this issue would be important to understand the genetic share of NPC among those population. In the present report, we evaluate and summarize a nucleotide sequence-level alleles of HLA class I and II loci in nineteen southern groups of East Asian populations. The genetic affinities of those populations and the specific haplotypes associated with nasopharyngeal carcinoma from ten genotypic data-populations are discussed.

Methods

This study was a retrospective study during a period 2005–2015 and was conducted using 19 southern groups of East Asian population data taken from/gathers by.

The HLA allele frequency at four digit level for HLA-A, -B and -DRB1 were obtained from nineteen populations both from previous studies {Javanese (Indonesia),[7] Kihn (Vietnamese),[20] Han (Yunnan, China),[21] Maonan (Guangxi, China),[22] Dai (Yunnan, China),[23] Hani (China),[24] Bulang (China),[24] Jinuo (China),[25] and Wa (China)[25]} and from www.allelefrequencies.net {Malay, Han (Singapore), Thai, Han (Yunnan, China), Jinuo (China), Wa (Yunnan, China), Han (Hong Kong), Han (Guangdong, China), Taiwanese, Han (Fengyuandong, China), Maonan (Guangxi, China), Buyi (China), Nu (China), and Lisu (Yunnan, China)}. Only populations with minimum sample size of 100 individuals were selected (Fig. 1).

Haplotype frequencies were estimated using the maximum likelihood method based on an expectation maximization algorithm with ARLEQUIN v.2.0 software (available from: http://anthro.unige.ch/arlequin/) with default setting. Genetic distances among 19 southern East Asians populations were calculated by the modified Cavalli-Sforza (DA) distance method.[26] A phylogenetic tree was constructed by the neighbor-joining (NJ) method using DISPAN software. Principal component analysis (PCA) was performed using XLSTAT-PRO software (http://www.xlstat.com).

Results

The most frequent HLA-A allele in all populations is A*11:01, except in Javanese (Indonesia) that placed in the second order. Among all selected populations, only Javanese (Indonesia), Malay and Bulang (China) have A*24:07 frequency more than 10%. The rest has less than 5% or even zero presence of A*24:07 (Table 1).

At the B locus, there was no specific pattern, except B*18:01 that is more frequent only in Javanese (Indonesia), Thai and Malay than in other southern East Asian populations. Some B alleles that showed frequencies >10% were B*40:01, B*46:01, B*13:01, B*15:02, and B*15:13 in some populations (Table 2).

At the DRB1 locus, DRB1*12:02 was the most frequent in Southeast Asian group and in specific populations live in Southern China, whereas the Taiwanese and southern Han populations exhibit DRB1*09:01 as the most frequent allele. Other DRB1 alleles that shows frequency >10% in at least 5 populations were DRB1*09:01, DRB1*15:01, DRB1*15:02, and also DRB1*12:02 (Table 3). Nineteen populations with sequence level allele frequencies were used for the principal component analysis (Fig. 1).

The obtained-DA distances among those populations were used for the phylogenetic tree analysis (Fig. 2). Those two results corresponded well. The southern East Asian populations in fact were also clustered into 2 major groups: the first is the southern Chinese Han populations, including Southeast Asian populations and the second is the specific ethnics live in Southern China (Fig. 3).

The estimated frequencies of haplotypes A33-B58-DR3, A2-B46-DR9, and their shared

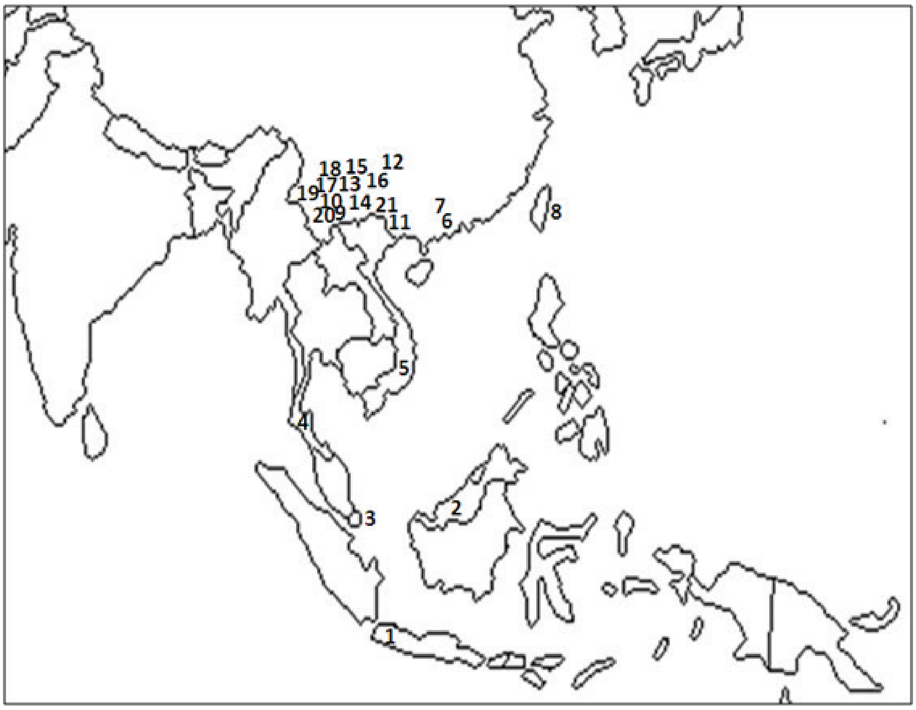

Figure 1 **Geographic Distribution of the Areas Resided by 20 Southern East Asian Populations**

Legends:

1 Javanese (Indonesia)
2 Malay
3 Han (Singapore)
4 Thai
5 Kihn (Vietnam)
6 Han (Hong Kong)
7 Han (Guangdong, China)
8 Taiwanese
9 Han (Yunnan, China)
10 Han (Fengyuandong, China)
11 Maonan (Guangxi, China)
12 Buyi (China)
13 Dai (Yunnan, China)
14 Bulang (China)
15 Jinuo (China)
16 Hani (China)
17 Wa (Yunnan, China)
18 Nu (Yunnan, China)
19 Lisu (Yunnan, China)

Table 1 Most Frequent HLA-A Alleles with Frequency ≥10% in at Least One Population

Population	n	A1101	A2402	A0201	A3303	A0207	A0203	A2407	Others
Javanese (Indonesia)	236	0.1603	0.1435	0.0696	0.1561	0	0.0422	0.2152	0.2131
Malay	1445	0.177	0.173	0.065	0.109	0.02	0.053	0.157	0.246
Han (Singapore)	149	0.265	0.154	0.104	0.101	0.131	0.067	0.01	0.168
Thai	142	0.299	0.039	0.018	0.127	0.109	0.077	0.046	0.285
Kinh (Vietnam)	170	0.229	0.138	0.021	0.115	0.085	0.079	0.044	0.289
Han (Hong Kong)	572	0.287	0.154	0.062	0.098	0.131	0.078	0.005	0.185
Han (Guangdong, China)	264	0.267	0.163	0.074	0.117	0.079	0.112	0.015	0.173
Taiwanese	710	0.2754	0.1704	0.1035	0.1035	0.0993	0.0732	0.0007	0.174
Han (Yunnan, China)	101	0.317	0.163	0.01	0	0.183	0.005	0	0.322
Han (Fengyuandong, China)	101	0.3168	0.1634	0.0099	0.0842	0.1832	0.005	0	0.2376
Maonan (Guangxi, China)	108	0.3519	0.1343	0.0463	0	0.1343	0.1759	0	0.1574
Buyi (China)	109	0.314	0.139	0.021	0	0.227	0.103	0	0.196
Dai (Yunnan, China)	124	0.3911	0.0807	0.0161	0.1008	0.1855	0.1089	0.0242	0.0927
Bulang (China)	116	0.5388	0.2371	0.0129	0.0086	0.0043	0.0819	0.1035	0.0129
Jinuo (China)	109	0.367	0.1835	0.0092	0.0229	0.1881	0.078	0.0046	0.1468
Hani (China)	150	0.5867	0.09	0.0333	0.0333	0.1067	0.0433	0.0033	0.1033
Wa (Yunnan, China)	119	0.584	0.1303	0.0084	0.1597	0.0084	0.0546	0.0084	0.0462
Nu (Yunnan, China)	107	0.481	0.114	0.089	0.044	0.082	0.082	0	0.108
Lisu (Yunnan, China)	111	0.461	0.118	0.085	0.011	0.022	0.152	0.006	0.145

n=sample size

Table 2 Most Frequent HLA-B Alleles with Frequency ≥10% in at Least One Population

Population	n	B4001	B4601	B5801	B1301	B1502	B1513	B5201	B1532	B1801	A2407	Others
Javanese (Indonesia)	236	0.0359	0	0.057	0.0148	0.116	0.1118	0.0105	0.0084	0.0422	0.0633	0.5823
Malay	1445	0.058	0.015	0.05	0.054	0.084	0.069	0.03	0	0.053	0.098	0.542
Han (Singapore)	149	0.172	0.132	0.104	0.084	0.057	0.003	0.017	0	0.067	0.007	0.424
Thai	142	0.085	0.092	0.066	0.021	0.085	0.018	0.034	0.011	0.077	0.067	0.521
Kinh (Vietnam)	170	0.062	0.115	0.063	0.038	0.135	0	0.003	0	0.079	0.006	0.578
Han (Hong Kong)	572	0.152	0.162	0.072	0.078	0.102	0	0.006	0.001	0.078	0.001	0.426
Han (Guangdong, China)	264	0.144	0.119	0.089	0.068	0.073	0	0.006	0	0.112	0.009	0.492
Taiwanese	710	0.2197	0.1261	0.0979	0.0528	0.0415	0	0.0106	0	0.0732	0	0.4514
Han (Yunnan, China)	101	0.045	0.198	0.069	0.045	0.124	0	0.005	0	0.005	0	0.514
Han (Fengyuandong, China)	101	0.0446	0.198	0.0743	0.0446	0.1238	0	0.005	0	0.005	0	0.5099
Maonan (Guangxi, China)	108	0.1343	0.1343	0.0417	0.1991	0.1482	0	0	0	0.1759	0	0.3426
Buyi (China)	109	0.103	0.191	0.083	0.103	0.155	0	0	0	0.103	0	0.365
Dai (Yunnan, China)	124	0.0565	0.254	0.0766	0.125	0.0686	0	0.0282	0.004	0.1089	0.0161	0.371
Bulang (China)	116	0.0905	0.0086	0.0043	0.0086	0.3448	0	0.056	0.0172	0.0819	0	0.4698
Jinuo (China)	109	0.0917	0.1468	0.0046	0.1606	0.2385	0	0.0092	0.0092	0.078	0	0.3395
Hani (China)	150	0.1	0.1633	0.0267	0.0167	0.1067	0	0.18	0.0533	0.0433	0	0.3533
Wa (Yunnan, China)	119	0.0882	0.0042	0.0168	0.021	0.2101	0	0.0336	0.1177	0.0546	0	0.5084
Nu (Yunnan, China)	107	0.122	0.09	0.019	0	0.09	0	0.186	0.064	0.082	0	0.429
Lisu (Yunnan, China)	111	0.072	0	0.007	0	0.123	0	0.231	0.058	0.152	0	0.509

n=sample size

Table 3 Most Frequent HLA-DRB1 Alleles with Frequency ≥10% in at Least One Population

Population	n	901	1501	803	1101	1602	1401	701	1502	1201	1202	1404	1504	Others
Javanese (Indonesia)	236	0.0211	0.0422	0.0063	0.0211	0.0316	0.0042	0.1308	0.23	0	0.3776	0.0169	0	0.1181
Malay	1445	0.046	0.12	0.028	0.046	0.028	0.009	0.083	0.12	0.028	0.324	0.037	0	0.131
Han (Singapore)	149	0.154	0.133	0.057	0.113	0.069	0.021	0.029	0.007	0.04	0.084	0	0	0.293
Thai	142	0.087	0.069	0.029	0.04	0.029	0.033	0.145	0.112	0.007	0.185	0.011	0	0.253
Kinh (Vietnam)	170	0.097	0.038	0.041	0.015	0.016	0.032	0.076	0.062	0.009	0.353	0.018	0	0.243
Han (Hong Kong)	572	0.126	0.109	0.047	0.027	0.008	0.042	0.128	0.034	0.115	0.108	0.014	0	0.242
Han (Guangdong, China)	264	0.144	0.108	0.059	0.07	0.051	0.017	0.057	0.053	0.028	0.133	0.002	0	0.278
Taiwanese	710	0.15	0.09	0.08	0.08	0.06	0.04	0.02	0.02	0	0	0	0	0.46
Han (Yunnan, China)	101	0.283	0.056	0.03	0.015	0.015	0.03	0.015	0.045	0.081	0.217	0	0	0.213
Han (Fengyuandong, China)	101	0.2828	0.0556	0.0303	0.0152	0.0152	0.0303	0.0152	0.0455	0.0808	0.2172	0	0	0.2121
Maonan (Guangxi, China)	108	0.0926	0.1064	0.0509	0.0232	0.1296	0.1064	0	0.0648	0	0.171	0.009	0	0.2461
Buyi (China)	109	0.084	0.154	0.029	0.054	0.148	0.169	0.007	0.043	0.014	0.083	0	0	0.215
Dai (Yunnan, China)	124	0.1169	0.0927	0.004	0.0202	0.1532	0.1089	0.0081	0.1331	0	0.0968	0.0323	0.004	0.2299
Bulang (China)	116	0.0129	0.0776	0.0129	0	0.0216	0.0302	0.0043	0.1207	0	0.556	0.0043	0.0431	0.1164
Jinuo (China)	109	0.0138	0.0413	0.0826	0.0367	0.0046	0.1697	0.0138	0.1927	0	0.3624	0.0046	0.0046	0.0734
Hani (China)	150	0.0267	0.0433	0.03	0.0133	0.0133	0.21	0.0033	0.07	0.0033	0.32	0.1167	0.07	0.08
Wa (Yunnan, China)	119	0.0042	0.0966	0.0378	0.0084	0.0042	0.0126	0.0546	0.084	0	0.3193	0.0672	0.1345	0.1765
Nu (Yunnan, China)	107	0.023	0.054	0.144	0.027	0.005	0.09	0.005	0.063	0.009	0.225	0.05	0.095	0.21
Lisu (Yunnan, China)	111	0.021	0.068	0.167	0.021	0	0.104	0	0.057	0.005	0.229	0.125	0.036	0.167

n=sample size

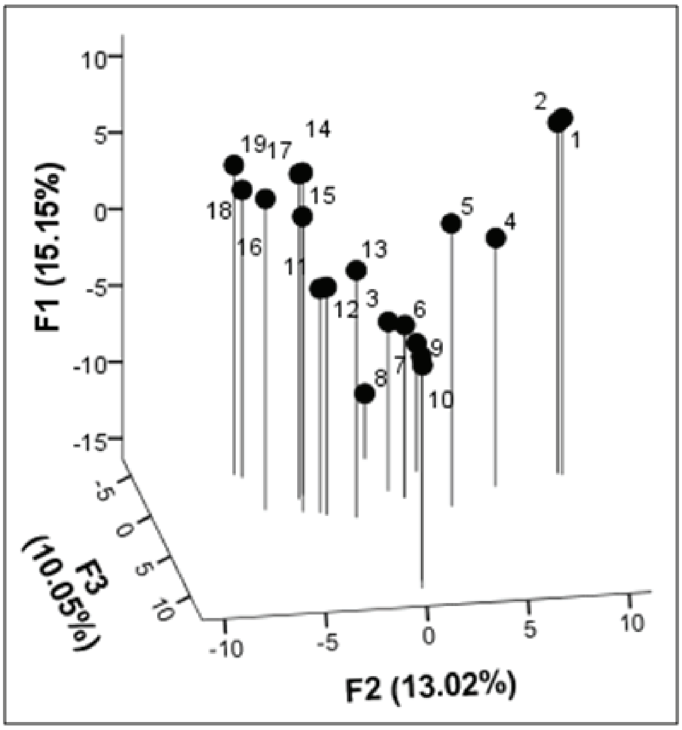

Figure 2 **Principal Component Analysis of Southern East Asian Populations (Axis F1, F2, and F3: 38.22%)**

Legends:

1	Javanese (Indonesia)	8	Taiwanese	15	Jinuo (China)
2	Malay	9	Han (Yunnan, China)	16	Hani (China)
3	Han (Singapore)	10	Han (Fengyuandong, China)	17	Wa (Yunnan, China)
4	Thai	11	Maonan (Guangxi, China)	18	Nu (Yunnan, China)
5	Kihn (Vietnam)	12	Buyi (China)	19	Lisu (Yunnan, China)
6	Han (Hong Kong)	13	Dai (Yunnan, China)		
7	Han (Guangdong, China)	14	Bulang (China)		

derivative haplotypes are listed in Table 4. The minor haplotypes were presented by the single B allele. Haplotypes A33-B58-DR3 was most frequently observed in Maonan and Dai. Haplotypes A2-B46-DR9/DR14 was commonly observed in Maonan, Dai, Jinuo, and Hani.

Discussion

Populations with close genetic affinity generally show similar HLA alleles and also haplotype frequencies that may related to HLA related disease distribution. In this study we analyzed and summarized a nucleotide sequence-level alleles of HLA class I and II loci in nineteen southern groups of East Asian populations and the genetic affinities of those populations and see the distribution of the specific haplotypes associated with nasopharyngeal carcinoma from 10 available genotypic data-populations. The pattern of HLA class I and II allele distribution among Southern East Asian may also be relevant to the disease distribution in the regions. HLA genes has been most extensively studied to be associated with NPC. It is postulated that individuals who carry particular HLA alleles might be at an increased risk for susceptibility or protection to NPC. It is because particular HLA molecule may increase or decrease the ability to present EBV antigens to the immune system.

In this study, based on the allele frequencies, the most frequent HLA-A allele in all populations is A*11:01, except in Javanese (Indonesia) that placed in the second order. This allele has been reported to be associated with a reduced risk for NPC in Southern Chinese descent.[14] Populations with Southern Chinese descent used in this study were Javanese (Indonesia), Malay, Han (Singapore), Thai, Kihn (Vietnam), Han (Hong Kong), Han (Guangdong, China), Taiwanese,

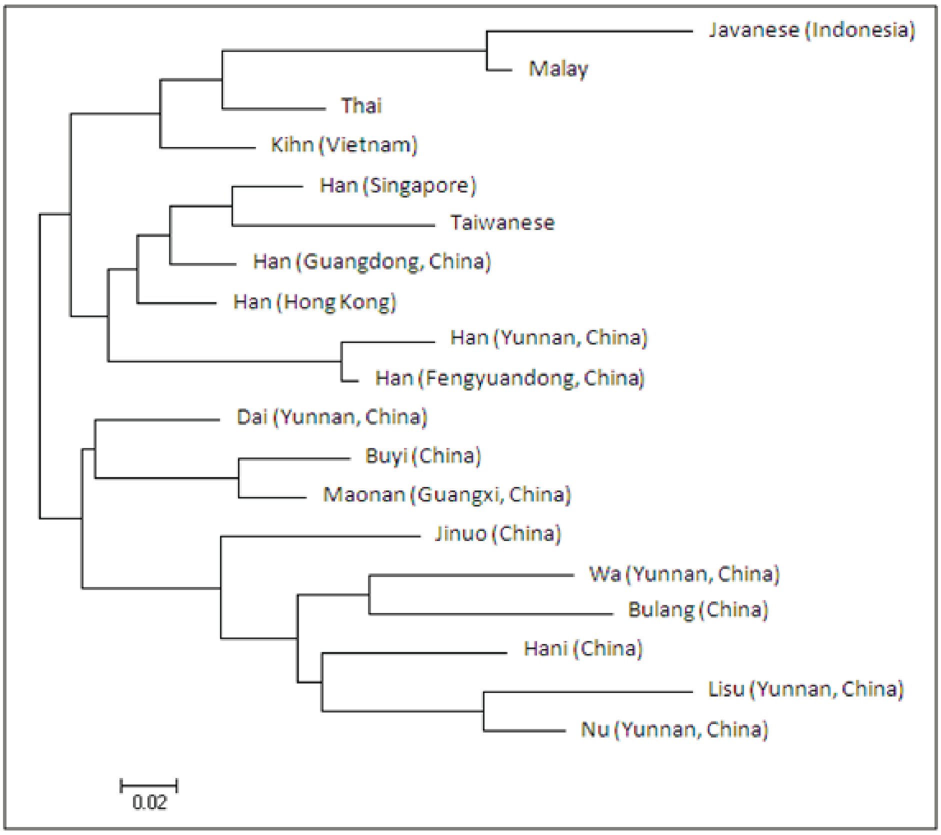

Figure 3 **Phylogenetic Tree Analysis of Southern East Asian Populations**

Legends:

- Southeast Asian populations: Javanese (Indonesia), Malay, Thai, Khin (Vietnam)
- Southern Han populations: Han (Singapore), Taiwanese, Han (Guangdong, China), Han (Hong Kong), Han (Yunnan, China), Han (Fengyuandong, China)
- Specific populations live in Southern China: Dai (Yunnan, China), Buyi (China), Maonan (Guangxi, China), Jinuo (China), Wa (Yunnan, China), Bulang (China), Hani (China), Lisu (Yunnan, China), Nu (Yunnan, China)

Han (Yunnan, China), Han (Fengyuandong, China), Maonan (Guanxi, China), Buyi (China), Dai (Yunnan, China), Bulang (China), Jinuo (China), Hani (China), Wa (Yunnan, China), Nu (Yunnan, China), Lisu (Yunnan, China), and Naxi (Yunnan, China).

At the B locus among the most frequent alleles (-B*40:01, B*46:01, B*13:01, B*15:02, and B*15:13), only HLA-B*46:01 that has been commonly reported to be associated with NPC in Chinese descendent populations.[14] The other HLA-B were reported to be associated with other diseases, but only reported in a few population. HLA-B*15:02 has been commonly associated with Carbamazepine induced severe adverse drug reaction in Southern China population group.[27] HLA-B*13:01 has been associated with the development of dapsone hypersensitivity syndrom in patients with leprosy in the Chinese population.[28] It was also reported to be associated with salazosulfapyridine-induce drug rashes with eosinophilia and systemic symptomps in Chinese Han population.[29] Studied in Thailand showed that HLA-B*40:01 has been associated with stavudine-associated lipodystrophy in HIV-infected patient.[30]

Among the most frequent DRB1 alleles (DRB1*09:01, DRB1*15:01, DRB1*15:02, and DRB1*12:02), none is reported to be associated with NPC. The disease associated with those most frequent DRB1 alleles are systemic lupus erythematosus and rhematoid arthritis in Japanese Population,[31] grave disease in Chinese Han population in Taiwan,[32] coronary artery disease in shouthern Han Chinese[33] and systemic sclerosis, which is autoantibody disease, in Chinese.[34]

In the principle component analysis, two

Table 4 Estimated Frequencies of A33-B58-DR3, A2-B46-DR9, and Their Derivative Haplotypes

Population	Sample Size	A33/Others-B58-DR3/Others				A2/Others-B46-DR9/14/Others			
		A	B	DR	Freq.	A	B	DR	Freq.
Javanese (Indonesia)	236	33	58	3	0.021				
		33	58	Others	0.029				
		Others	58	Others	0.006				
Kihn (Vietnam)	170	33	58	3	0.038	2	46	9	0.031
		Others	58	Others	0.027	2	46	Others	0.036
						Others	46	Others	0.047
Han (Yunnan, China)	101	33	58	Others	0.041	2	46	Others	0.036
		Others	58	Others	0.018	Others	46	Others	0.141
Maonan (Guangxi, China)	108	33	58	3	0.036	2	46	9	0.045
		Others	58	Others	0.005	2	46	14	0.051
						2	46	Others	0.039
Dai (Yunnan, China)	124	33	58	3	0.044	2	46	9	0.071
		33	58	Others	0.032	2	46	14	0.069
						2	46	Others	0.049
						Others	46	Others	0.065
Bulang (China)	116	Others	58	Others	0.004	Others	46	Others	0.008
Jinuo (China)	109	Others	58	Others	0.005	2	46	14	0.063
						2	46	Others	0.083
Hani (China)	150	33	58	Others	0.027	2	46	14	0.064
						2	46	Others	0.019
						Others	46	Others	0.08
Wa (Yunnan, China)	119	33	58	3	0.017	Others	46	Others	0.004
Naxi (Yunnan, China)	75	Others	58	Others	0.007	2	46	Others	0.04
						Others	46	Others	0.026

Freq: Estimated haplotype frequency

clusters were observed. It may also reflect the migration history of Southern East Asian populations, regardless the north-to-south or south-to-north migration route theory. Southeast Asian populations are closer to Southern Han Chinese populations than to the specific ethnics live in Southern China. A study in Indonesia by Yuliwulandari et al. (2008)[7] reinforces the PCA result in this study.

At the haplotype level, haplotype A35-B58-DR3, reportedly to be strictly associated with NPC.[18,20] This haplotype is commonly found among general population. With those regard, the estimated frequencies of this haplotype in different populations using the maximum likelihood method are reliable for presuming the susceptibility to the disease in each population in Southern East Asia. B58 carrying haplotypes predominantly include specific alleles, A33 and DR3. Thus, the haplotype containing B58 may have been well conserved. However, it should be understood that if NPC is associated with variant haplotypes derived from the A35-B58-DR3 haplotype, further family studies to discribe more precise di-haploidy information are needed to define susceptibility gene(s). The minor haplotypes were presented by the single B allele, considering that inferring haplotype using maximum likelihood method is not reliable for those infrequent haplotypes. Dai and Maonan populations carried both haplotypes.[22,23]

Haplotype A2-B46-DR9, which has been found to be associated with autoimmune thyroid dysfunction in Chinese was less frequent in all southern East Asian populations.[19] B46 is also frequently linked to DR14, such as in Jinuo (China) (f=0.063), Maonan (Guangxi, China) (f=0.051), Dai (Yunnan, China) (f=0.069). Other less frequent derivative haplotypes containing B46 were also frequently observed. Thus, B46 haplotypes have been relatively more diversified than B58 haplotypes. Considering that A2-B46 was also frequently linked to both DR14 and DR9, it is possible that A2-B46-DR14 may also be related to NPC in this southern East Asian population group. Further study is needed to confirm this assumption. The limitation of this study were that we did not analyze the role of the HLA haplotype directly in NPC patients in Indonesia, in which Indonesia showed the intermediate incidence rates of NPC.[13] Therefore in the future we need to apply the result of this study in the population to screen NPC in Indonesia population.

Conclusion

HLA allele(s) and haplotype distribution shows the closeness of genetic relationship among populations. Those distributions tend to affect disease distribution in the population, including NPC. In NPC, HLA haplotype sharing is more important than HLA allele sharing. The A33-B58-DR3 haplotype and A2-B46-DR9 haplotype in this study could be related to NPC, especially in the Southern East Asian populations group. The observed haplotype needs to be tested in the real patients to confirm the susceptibility of the haplotype in Indonesia.

Conflict of Interest

The authors declare no conflict of interests.

Acknowledgement

We would like to thank the late Prof. Malcolm Simons for useful discussion and Ms. Kinasih Prayuni for editing the manuscript.

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