

# Polymorphisms of human leucocyte antigen genes in Maonan people in China

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## Key words

HLA-A; HLA-B; HLA-DRB1; haplotypes; Maonan population

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## Abstract

We examined human leucocyte antigen (HLA) gene polymorphisms in the Maonan people from southern China. HLA-A, -B and -DRB1 alleles were determined in 108 healthy unrelated Maonan individuals by the polymerase chain reaction-Luminex method, and haplotype frequencies for HLA-A, -B and -DRB1 loci were estimated. The most frequent HLA-A alleles were A\*1101 (35.2%), A\*0203 (17.6%), A\*0207 (13.4%) and A\*2402 (13.4%); HLA-B alleles were B\*1301 (19.9%), B\*1502 (14.8%), B\*4601 (13.4%) and B\*4001 (13.4%); HLA-DRB1 alleles were DRB1\*1202 (17.1%), DRB1\*1602 (13.0%) and DRB1\*1401 (10.7%). The most common haplotypes were A\*0207-B\*4601 (10.6%), A\*1101-B\*1301 (10.0%), A\*1101-B\*4001 (8.4%), B\*1502-DRB1\*1202 (12.0%), B\*4601-DRB1\*1401 (5.8%), A\*1101-B\*1502-DRB1\*1202 (7.1%) and A\*0207-B\*4601-DRB1\*1401 (5.3%), profiles that are also found in populations from the southern region of East Asia. Phylogenetic and principal component analyses revealed that the Maonan people belong to the southeastern Asian group and are most closely related to the Buyi people.

## Introduction

The Maonan people, one of 55 official ethnic minorities in China, number approximately 107,000. The Maonan families are generally small and monogamous, with the same surnames, and are from the same clans usually living

together in small villages with only a few households. The biggest village consists of not more than 100 households. The major staples of the Maonans are rice and maize, followed by millet, sweet potatoes and pumpkins. The language of the Maonan people belongs to the Dong-Shui branch of the Zhuang-Dong language group of the Chinese-Tibetan language family. Most members of the tribe inhabit the area around the Maonan Mountain of Huangjiang Country in the Guangxi Province of the Zhuang Autonomous

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Region in Southern China (Figure 1). The three districts of Shangnan, Zoungnang and Xianan have been referred to as 'San Nan Shan Xiang' since early times, which means 'Maonan village in a mountain valley'. The Maonan people call themselves 'Anan', meaning 'indigenous people', which suggests that they are indigenous to the area. According to historical evidence, the Maonan people have descended from the ancient tribes of the 'Baiyue' and 'Liao' and that the Maonan tribe formed by amalgamating with some other population (1).

The major histocompatibility complex (MHC) is an extremely hypervariable region of genomic deoxyribonucleic acid (DNA), which is approximately four megabases in size and located on the short arm of chromosome 6. The region plays an important role in the immune response and displays marked degree of genetic polymorphism. The human MHC is known as the human leucocyte antigen (HLA) system, which contains three gene regions: class I, class II and class III. Class I and II genes are among the most polymorphic regions characterized in the human genome to date. Approximately 1700 alleles in the regions containing HLA classes I and II have been identified around the world. HLA allele and haplotype frequencies have been reported to vary considerably among different ethnic groups (2, 3), and the HLA characteristics of many ethnic populations have been investigated to elucidate their origins and evolutionary relationships (2–4).

The purpose of our study was to determine the frequencies of the HLA class I and class II alleles and their haplotypes in the Maonan population using the polymerase chain reaction (PCR)-Luminex method. The results were compared with those obtained from other East Asian populations by phylogenetic analysis and principal compo-

nent analysis (PCA). In addition, we also discuss the distribution of HLA alleles in the Maonan population within the context of hypothesis of their ancestry tribe.

## Materials and methods

### Samples

Blood samples were collected from a total of 108 unrelated healthy Maonan adults at Xianan village of Huangjiang Country in the Guangxi Province, all of whom gave written informed consent. Genomic DNA was extracted from peripheral lymphocytes by a standard hydroxybenzene-chloroform method.

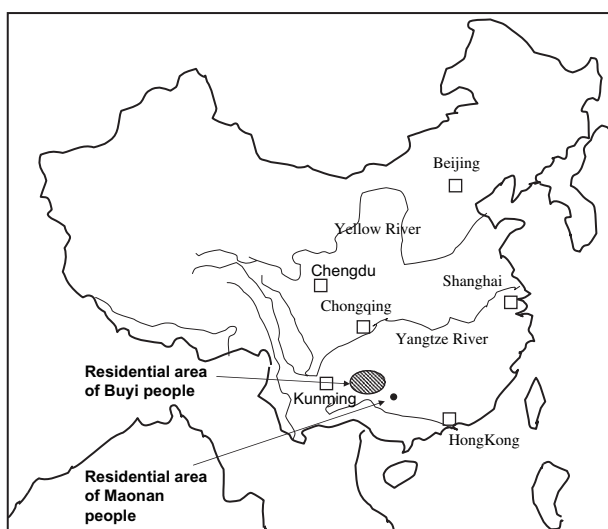
### HLA-A, -B and -DRB1 allele typing

HLA-A, -B and -DRB1 polymorphisms were examined using a WAKFlow HLA typing kit (Wakunaga, Hiroshima, Japan), which is based on PCR-sequence specific oligonucleotide probing coupled with multiple analyte profiling technology, 'Luminex system' (5, 6). All the assignments were obtained with high levels of resolution, and the entire process was performed in a single well of a 96-well PCR plate, implying that 96 samples could be treated at the same time. The HLA alleles were determined by analysis of the reaction (hybridization) pattern of the target sample. The ambiguities encountered using this method were rare, and the technique was simple and efficient to perform.

Given that several atypical hybridization patterns were observed, some of the samples were examined by direct sequencing. We performed cycle sequencing (3100 Genetic Analyzer, Applied Biosystems, Tokyo, Japan) using a Big-dye Terminator kit after Sephadex<sup>TM</sup> G-50 purification.

### Statistical analysis

Haplotype frequencies were estimated using the maximum likelihood method based on an expectation maximization algorithm (7) with ARLEQUIN software (<http://anthro.unige.ch/arlequin/>), (8). Nei's standard genetic distances (9) among 18 East Asian and German populations were calculated based on the HLA-A, -B and -DRB1 allele frequencies. Using these distances, a phylogenetic tree was constructed by the neighbor-joining method (10). PCA was performed using HLA-A, -B and -DRB1 allele frequencies for 14 East Asian populations (the other four populations were omitted because class I and II data were obtained from different individuals) by JMP software (SAS Institute, Tokyo, Japan). Allele and haplotype frequencies in other East Asian populations and German population were obtained from previous studies: German (11), Korean (North China), South Korean, Chinese Man, Japanese and Mongolian (12), Chinese Buyi (13), Chinese Tibetan (14), Chinese Xibai Han (15, 16), Chinese (Singapore) (13, 17),



**Figure 1** Geographic distribution of the areas inhabited by Maonan and Buyi people.

Chinese Xiamen Han (18), Taiwanese (19), Thai (20), Vietnamese (21, 13), Chinese (Hong Kong) (17, 22), Chinese Wuhan Han (23) and Chinese Naxi and Yunnan Han (24). Some haplotype data were obtained from the 11th International Histocompatibility Workshop and Conference Reference tables and the 12th International Histocompatibility Workshop IX Anthropology tables (13, 25).

## Results and discussion

The estimated allele frequencies are shown in Table 1. A total of 9 HLA-A, 23 HLA-B and 20 HLA-DRB1 alleles, which correspond to 4 HLA-A, 14 HLA-B and 7 HLA-DR serological specificities, respectively, were found in the 108 individuals examined. No new alleles were detected.

### HLA-A alleles

Three of the HLA-A allele groups were present at frequencies greater than 10%: HLA-A\*11 (41.7%), A\*2 (40.3%) and A\*24 (13.9%). Of the HLA-A allele groups assayed, maximum variation was observed in HLA-A\*02 (A\*0201, A\*0203, A\*0206, A\*0207). At the HLA-A locus, four alleles were present at frequencies exceeding 10%:

HLA-A\*1101 (35.2%), A\*0203 (17.6%), A\*0207 (13.4%) and A\*2402 (13.4%). A total of 15.8% (17/108) of the samples were homozygous at the sequence level, and the observed heterozygosity was 84.2%.

Of all the HLA-A groups studied globally to date, A11 is one of the most common and is highly prevalent in Southeast Asia (26–29). As in other Asian populations, HLA-A11 allelic variants observed in this study were found to be encoded by the A\*1101 and A\*1102 alleles (predominantly by A\*1101) (17, 30, 31). A\*02 has also been reported to be prevalent among many populations (3, 32, 33). Four alleles, A\*0201, A\*0203, A\*0206 and A\*0207, were detected in this study, with the HLA-A02 allelic variants predominated by A\*0203 and A\*0207, although A\*0201 was also prevalent in many populations (34–37). A\*0206 was found to be common in most Asian populations (25, 38), whereas A\*0203 and A\*0207 were common in the Southern Asian populations (34, 38). Two A24 alleles (A\*2402 and A\*2403) were detected in this study, with A\*2402 occurring more frequently (13.4%) than A\*2403 (0.5%). A\*2402 was common in other Asian populations (17, 39–42). On A33 group, only one allele (A\*3303) was detected in this study. A\*3303 occurs commonly in Asian populations (25, 30, 39–41).

**Table 1** Human leucocyte antigen (HLA)-A, -B and -DRB1 allele frequencies in the Maonan population

HLA-A*	Allele frequency (2n = 216)	HLA-B*	Allele frequency (2n = 216)
A*0201	0.046	B*0801	0.005
A*0203	0.176	B*1301	0.199
A*0206	0.046	B*1501	0.014
A*0207	0.134	B*1502	0.148
A*1101	0.352	B*1505	0.005
A*1102	0.065	B*1525	0.009
A*2402	0.134	B*2704	0.028
A*2403	0.005	B*2706	0.005
A*3303	0.042	B*3501	0.005
HLA-DRB1*		B*3802	0.083
DRB1*0301	0.046	B*3901	0.028
DRB1*0403	0.009	B*3915	0.005
DRB1*0404	0.009	B*4001	0.134
DRB1*0405	0.088	B*4002	0.028
DRB1*0406	0.005	B*4601	0.134
DRB1*0803	0.051	B*4801	0.005
DRB1*0901	0.093	B*5101	0.019
DRB1*1101	0.023	B*5102	0.005
DRB1*1202	0.171	B*5401	0.019
DRB1*1303	0.069	B*5501	0.005
DRB1*1501	0.106	B*5502	0.06
DRB1*1401	0.106	B*5601	0.019
DRB1*1404	0.009	B*5801	0.042
DRB1*1405	0.014		
DRB1*1502	0.065		
DRB1*1601	0.005		
DRB1*1602	0.130		

### HLA-B alleles

At HLA-B, four allele groups were present at frequencies greater than 10%: HLA-B\*13 (19.9%), B\*15 (17.6%), B\*40 (16.2%) and B\*46 (13.4%). Four alleles were present at a frequencies greater than 10%: HLA-B\*1301 (19.9%), B\*1502 (14.8%), B\*4601 (13.4%) and B\*4001 (13.4%). A total of 13.0% (14/108) of the samples were homozygous at the sequence level, and the observed heterozygosity was 87.0%. The B13 allele, B\*1301 (19.9%), has been reported to be common in other Asian populations (43). Both B\*1301 and B\*1302 were predominantly detected in northern and southern Chinese, with the former being more common than the latter among southern Chinese compared with northern Chinese (44). Interestingly, B\*1301 has been reported to be associated with resistance to severe acute respiratory syndrome (SARS) coronavirus infection (45). Four B15 alleles (B\*1501, B\*1502, B\*1505 and B\*1525) were detected in this study; B\*1502 (14.8%) was the most common allele in Southeast Asian and Japanese populations (46). In this study, two B40 alleles were detected, B\*4001 and B\*4002, while B\*4001 (13.4%) was well represented and is commonly found in Asian populations (17, 44). The only B46 allele was B\*4601 (13.4%), which occurs at high frequencies in Southeast Asia (Southern Han: 15.4%; Singaporean: 15.1% and Vietnamese: 13.2%) (47). Moreover, B\*4601 has been reported to be a susceptibility allele for SARS coronavirus infection, which might be the reason why southern China was the epicenter of the SARS epidemic (45).

### HLA-DRB1 alleles

Four HLA-DRB1 alleles occurred at frequencies greater than 10% at the sequence level: HLA-DRB1\*1202 (17.1%), DRB1\*1602 (13.0%), DRB1\*1401 (10.7%) and DRB1\*1501 (10.7%). DRB1\*1401 and DRB1\*1501 were found in many populations, while DRB1\*1202 and DRB1\*1602 were commonly found in other Southeast Asian populations (47, 48). At the HLA-DRB1 locus, 6.5% (7/108) of donors were homozygous at the sequence level, and the observed heterozygosity was 83.5%.

### Haplotype frequencies

In the analysis of HLA-A-B and HLA-B-DRB1 haplotype frequencies, 14 and 16 haplotypes were observed at frequencies of more than 2%, respectively (Table 2). In the analysis of HLA-A-B-DRB1 haplotype frequencies, 13 haplotypes were observed at frequencies of more than 2% (Table 3).

Two HLA-A-B haplotypes occurred at frequencies greater than 10%: HLA-A\*0207-B\*4601 (10.6%) and HLA-A\*110101-B\*1301 (10.0%). A02-B46 and A11-B13 have commonly been observed in other East Asian populations (A02-B-46: Buyi, Miao, Japanese, South Korean, Northern Han, Southern Han; A02-B-13: North East Thai, Northern Han, Southern Han, Buyi, Miao and Man).

Four HLA-A-B-DRB1 haplotypes occurred at frequencies exceeding 5%: HLA-B\*1502-DRB1\*1202 (12.0%), HLA-B\*4601-DRB1\*1401 (5.8%), HLA-A\*1101-B\*1502-DRB1\*1202 (7.2%) and HLA-A\*0207-B\*4601-DRB1\*1401 (5.3%). HLA-B15-DRB1\*1202 and HLA-B46-DRB1\*1401 have commonly been observed in other East Asian populations (B15-DRB1\*1202: Naxi,

Yunnan Han, Man, Korean (North China); HLA-B46-DRB1\*1401: Naxi and Yunnan Han). HLA-A11-B15-DRB1\*1202 was common in Naxi and White Thai, and A02-B46-DRB1\*1401 was common in White Thai.

We found that all the allele frequencies for HLA-A, HLA-B and HLA-DRB1 in Maonan group were also found in other Southeast Asian groups. In addition, the haplotype frequencies of the Maonan people were similar to those found in other East Asian populations, indicating that the Maonan people belong to the southeastern Asian group.

### Analyses on genetic affinities

The phylogenetic tree in Figure 2 was constructed using Nei's standard genetic distances and was based on the gene frequencies of HLA-A, -B and -DRB1 for 18 East Asian and 1 Caucasian population. Caucasian German was placed on farthest distance from East Asian populations. Southeastern and northeastern Asian groups branched off at the middle of phylogenetic tree, but only the Yunnan Han group, who live in southwest of China, was closely affiliated to the northeastern Asian clusters.

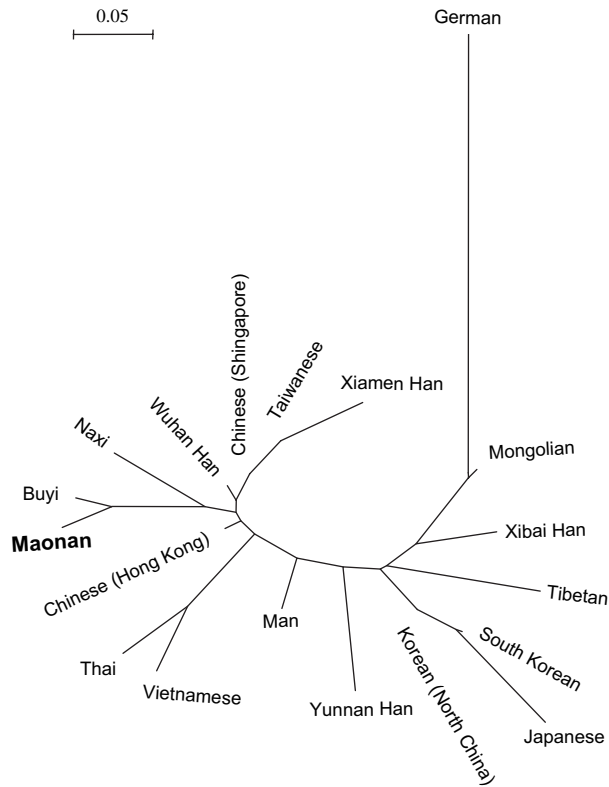
Figure 3 shows the results obtained from the PCA of 14 East Asian populations based on allele frequencies at the HLA-A, -B and -DRB1 loci. Contributions of the first and second principal components were 16.9% and 13.6%, respectively (30.4% total). In the analysis, the Maonan group was closest to the Buyi group. The Southeast Asian groups (Thai, Xiamen Han, Taiwanese, Naxi and Buyi) formed a cluster with the northeastern Asian groups (Japanese, South Korean, Korean (North China), Man and Mongolian). The Yunnan Han grouped in the middle of the northern and southern clusters of East Asian populations. Maonan people were clearly strongly associated with the southern clusters of East Asian populations, and this relationship may be reflected by the geographic distribution of these.

**Table 2** Most common human leucocyte antigen (HLA)-A-B and HLA-B-DRB1 haplotypes in the Maonan population

HLA-A-B haplotypes	Frequency (%)	HLA-B-DRB1 haplotypes	Frequency (%)
A*0207 B*4601	10.6	B*1502 DRB1*1202	12.0
A*1101 B*1301	10.0	B*4601 DRB1*1401	5.8
A*1101 B*4001	8.4	B*1301 DRB1*0405	4.5
A*1101 B*1502	7.7	B*5801 DRB1*0301	4.2
A*0203 B*3802	6.0	B*4601 DRB1*0901	3.9
A*0203 B*5502	5.0	B*1301 DRB1*1502	3.4
A*2402 B*1301	4.4	B*1301 DRB1*1202	2.8
A*0203 B*1502	4.1	B*3802 DRB1*0803	2.8
A*3303 B*5801	3.6	B*4001 DRB1*1501	2.7
A*2402 B*4001	3.5	B*4001 DRB1*0901	2.7
A*0201 B*1301	3.1	B*1301 DRB1*1602	2.6
A*1101 B*4002	2.8	B*3802 DRB1*1501	2.3
A*1102 B*2704	2.8	B*3901 DRB1*1602	2.3
A*1102 B*3901	2.3	B*4001 DRB1*0803	2.3
		B*4002 DRB1*1602	2.3
		B*5502 DRB1*1602	2.3

**Table 3** Most common human leucocyte antigen (HLA)-A-B-DRB1 haplotypes in the Maonan population

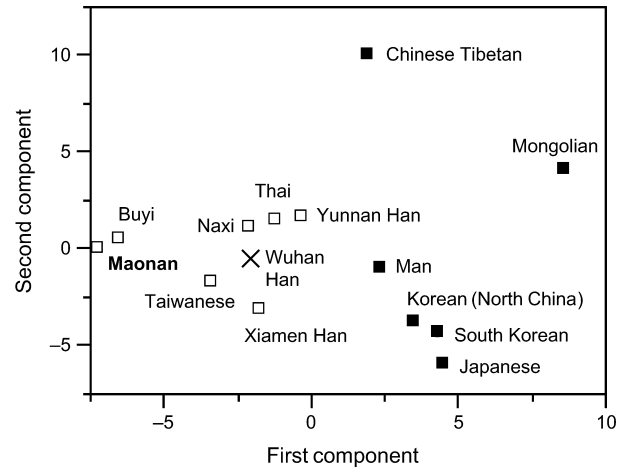
Haplotypes	Frequency (%)
A*1101 B*1502 DRB1*1202	7.2
A*0207 B*4601 DRB1*1401	5.3
A*3303 B*5801 DRB1*0301	3.7
A*0207 B*4601 DRB1*0901	3.6
A*0203 B*1502 DRB1*1202	3.2
A*0203 B*3802 DRB1*1501	2.8
A*0201 B*1301 DRB1*0405	2.7
A*0203 B*5502 DRB1*1303	2.3
A*1101 B*4002 DRB1*1602	2.3
A*1102 B*3901 DRB1*1602	2.3
A*1101 B*1301 DRB1*1202	2.1
A*2402 B*1301 DRB1*1502	2.1
A*1101 B*4001 DRB1*1602	2.0



**Figure 2** An affinity network constructed using Nei's standard genetic distance, and the allele frequencies of human leucocyte antigen (HLA)-A, -B and -DRB1 for 18 Asian and 1 Caucasian populations.

In the phylogeny analysis, Maonan group was closest to Buyi people, and then to Naxi, Chinese (Hong Kong) and Wuhan Han. Both the phylogenetic tree and PCA indicated that Maonan people belonged to the southeastern Asian group and were most closely related to the Buyi people from the Buyi and Miao Autonomous Regions in south Guizhou and Anshun. The Buyi people, with a population of approximately 2,545,000, live mostly on plains or in river valleys in villages composed of families from several different clans, in two-storied houses, bungalows or combination of the two. Maonan people descended from the 'Baiyue' and 'Liao' ancient tribes, while the Buyi people were indigenous to the Southeast Yunnan-Guizhou Plateau (Figure 1). The Buyi descended from the ancient 'Luoyue' and 'Liao' people and speak a language that belongs to the same linguistic group as the language of Maonan people, the Zhuang-Dong language group of the Chinese-Tibetan language family (1, 49). The phylogenetic tree constructed using HLA data revealed a close relationship between the Maonan and Buyi populations, supporting this linguistic evidence.

Phylogenetic analysis and PCA of the HLA data in this study suggest that there are two major groups, southern and northern groups, in East Asia and corroborate similar findings using Y-chromosome and mitochondrial DNA polymorphisms (50–52).



**Figure 3** Principal component analysis for human leucocyte antigen (HLA)-A, -B and -DRB1 allelic data was performed for the 14 East Asian populations (the other four populations were omitted because class I and II data were obtained from different individuals). From the border of Yangtze river, the southern group of the East Asian populations are represented by an open square (Maonan, Xiamen Han, Yunnan Han, Taiwanese, Thai, Naxi and Buyi), the northern group of the East Asian populations are represented by a closed square (Man, Mongolian, Chinese Tibetan, South Korean, Korean (North China) and Japanese). The populations located between these groups are represented by a cross (Wuhan Han).

In the PCA, the Yunnan Han was located between the northern and southern East Asian population clusters. Interestingly, despite residing in southwestern China, the Yunnan Han grouped with the populations in northeastern Asia. In our previous study (24), both common HLA haplotypes in Southeast Asian and those in Northeast Asian showed high frequencies in Yunnan Han population. Thus, considerable admixture might have existed between the Han population originated from the basin of the Yellow river and the local ethnic groups in Yunnan province since the migration of the Han population.

The marked variability of the HLA system makes it highly suited to population studies. The PCR-Luminex method using fluorescent microspheres made it possible to determine the genotypes of the HLA-A, -B and -DRB1 with the sequence level of resolution. Future research should attempt to increase sampling from various populations, typing of HLA gene polymorphisms and data collection for other genetic markers and historical records in order to infer Chinese ethnical admixture more accurately.

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