



Original Article

Deduced probable human leukocyte antigen haplotypes associated with human leukocyte antigen DRB1*04:36 identified by case analysis of Taiwanese individuals

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ABSTRACT

Objective: Human leukocyte antigen (HLA) DRB1*04:36 is a low-frequency HLA-DRB1 allele. The aim here is to report the ethnicity of DRB1*04:36 and its associated HLA haplotypes among Taiwanese individuals. **Materials and Methods:** A sequence-based typing method was employed to confirm this low incidence allele. Polymerase chain reaction was performed to amplify exons 2 and 3 of the HLA-A and HLA-B loci and exon 2 of the HLA-DRB1 locus using group-specific primer sets. The amplicons were sequenced in both directions using BigDye Terminator Cycle Sequencing Ready Reaction kits and the manufacturer's protocols. One group of unrelated blood donors used in this study consists of randomized individuals with Taiwanese ethnicity who participate in the Tzu Chi Bone Marrow Donor Registry and the other group are randomized unrelated individuals from mainland China. The family members in the family part of the study are volunteer blood donors. **Results:** In exon 2, the DNA sequence of DRB1*04:36 is identical to DRB1*04:03:01 except for a nucleotide segment from residue 286 to residue 308. The nucleotide segment from residue 286 to residue 308, incidentally, is identical to that of DRB1*11:01:01:01. These observations suggest that DRB1*04:36 may have been derived through a gene recombination event involving DRB1*04:03:01 and DRB1*11:01:01:01. Our family study indicated that the HLA haplotype in association with DRB1*04:36 can be deduced to be A*24:02-B*39:01-DRB1*04:36. A randomized population study using Taiwanese suggests that additional DRB1*04:36 associated HLA haplotypes seem to exist. **Conclusion:** The information on the ethnicity of the DRB1*04:36 allele, and the deduced probable HLA haplotypes associated with the low incidence DRB1*04:36 allele that we report here, is of value to HLA testing laboratories for reference purposes. In addition, they can be used by stem cell transplantation donor search coordinators to aid the creation of strategy for finding compatible donors who are part of unrelated bone marrow donor registries when a patient carries this uncommon HLA allele.

KEYWORDS: Anthropology, Chile, Libya, Mainland Chinese, Taiwanese

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INTRODUCTION

Transplantation of allogeneic hematopoietic stem cells has been employed as a curative therapy for hematological malignancies and other hematological or immune disorders. Human leukocyte antigen (HLA)

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molecules have been definitely defined as transplant antigens and have a strong relevance to tissue transplantation. The molecular similarity of these genes between transplant donors and recipients is considered a predictive factor for graft survival and graft versus host disease; this is because they can elicit immune responses either by recognition of polymorphic fragments of foreign HLA molecules or through the presentation of variable peptides [1,2]. The genes encoding the HLA alleles are located in the major histocompatibility complex Class I and II regions. HLA genes are characterized by their extreme allelic polymorphism as well as their variation and diversity across different ethnic groups [3].

Determination of HLA haplotype is essential when matching between donor and recipient for unrelated stem cell transplantation since this increases the likelihood of matching at other loci within the HLA region compared to when donors and recipients are merely matched at the individual allele level. Determination of HLA haplotypes may be accomplished by HLA typing of genetically related family members [4] and by prediction based on a large-sized population tissue typing [5-7]. Alternatively, it can be achieved by deduction using the typing results from donors with allelic homozygosities in the HLA-A, HLA-B, and HLA-DR loci [8]. In family studies, segregation of HLA individual alleles provides evidence of allelic linkage [4]. In population studies, determination of haplotypes involves noting whether alleles at the other two loci are consistently present and in such cases a family study is not performed. Instead, most available haplotype data are derived from studies of a population of unrelated individuals in whom the putative haplotype is defined by statistical association analysis [6,7].

The nucleotide sequence of HLA-DRB1*04:36 was first identified in a Taiwanese individual and submitted to the IMGT/HLA database in 2000 (ID: HC12137) [3]. In 2007, a second individual with DRB1*04:36 was discovered and reported by an Australian Laboratory (ID: HC14606) [3]. It was indicated that the Taiwanese individual bearing the allele was an indigenous individual from the Bunun tribe [3,9] while the ethnicity of the Australian blood donor is unknown [3]. Two probable DRB1*04:36 associated HLA haplotypes were speculated for the Bunun individual; these were either A*24:02-B*40:01-DRB1*04:36 or A*24:02-B39:01-DRB1*04:36 by Chu *et al.* [9] However, the Australian Laboratory did not speculate on the HLA haplotype of their individual carrying the DRB1*04:36 allele.

As HLA has been employed as a tool in anthropology for the study of human ethnicities, the discovery of rare

incidence alleles is useful in such a context because it opens up the possibility of studying the history of such populations, their migration, and possible integration events between populations. Here, we report the ethnicity of DRB1*04:36 and its associated HLA haplotype based on a family study and a randomized population study using a Taiwanese population. In addition, we discuss the possible mechanism whereby the allele may have come about.

MATERIALS AND METHODS

Peripheral whole blood samples from a Puyuma family that consisted of three members together with a range of unrelated blood donors with Taiwanese ethnicity and mainland Chinese ethnicity were collected in acid citrate dextrose (ACD) anticoagulant. Formal written consent was individually given by the donors before blood collection. The ACD whole-blood samples were stored at -80°C until use.

Peripheral blood genomic DNA was extracted using QIAamp DNA Blood Mini kits (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The DNA obtained was subjected to HLA genotyping for the HLA-A, HLA-B, HLA-DRB1, and HLA-DQB1 loci using commercial polymerase chain reaction sequence-based typing kits (Secore® A/B/C/DRB1 Locus Sequencing kits, Life Technologies, Brown Deer, WI, USA). High-resolution allelic sequencing was performed as previously described [10-13].

Two sets of primer sequences used were: (1) B-CG: M13-BIN1- CGG (sense): TG TAAAACGACGCGCCAGTCGGGGGCGCA GGACCCGG; P3' exon 5B (anti-sense): GCTCCG ATGACCACAACCTGCT and (2) B-TA: M13-BIN1-TGA (sense): TG TAAAACGACGCGCCAGTGGCGGGGGC GCAGGACCTGA; P3' exon 5B (anti-sense): GCTCCGATGACC ACAACCTGCT. The amplicons were then sequenced in both directions using a BigDye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems, Foster City, CA, USA) and the manufacturer's instructions [10-13].

Determination of the deduced probable DRB1*04:36 associated HLA haplotypes in this study was carried out by looking at the commonly shared HLA typing of the donors carrying DRB1*04:36 in a family under study and in a population made up of randomized unrelated blood donors [4,14].

RESULTS

We confirmed that, in exon 2, the DNA sequence of DRB1*04:36 observed was identical to that of

DRB1*04:03:01 except for the residues from 286 to 308 [Figure 1] [9]. The nucleotide segment from residue 286 to residue 308, incidentally, is identical to that of DRB1*11:01:01:01. This observation suggests that DRB1*04:36 may have been generated through a gene recombination event involving DRB1*04:03:01 and DRB1*11:01:01:01, wherein DRB1*11:01:01:01 has donated a section of its DNA sequence that consists at least of the sequence from position 286 to position 308 to the recipient allele DRB1*04:03:01 [Figure 1]. The recombination event resulted in DRB1*04:36, which has an amino acid sequence identical to DRB1*04:03:01 except for the amino acids from residue 67 to residue 74, which are the same as those present in DRB1*11:01:01:01 [Figure 2].

A total of 29,721 individual donors were tested for DRB1*04:36 using the mainland China randomized pool and we did not detect any donor carrying this allele. In a Taiwanese family study [Table 1], we found three Puyuma family members who carried DRB1*04:36 and we were able to deduce an HLA haplotype that was association with DRB1*04:36; this was A*24:02-B*39:01-DRB1*04:36. In addition, using the randomized Taiwanese unrelated blood donor pool that consisting of 167,597 individuals, we found 19 individuals who carried the allele (frequency =0.01%) [Table 2]. From these individuals' HLA typing, several probable DRB1*04:36 associated HLA haplotypes may be deduced; furthermore, among these deduced HLA haplotypes, several individuals were found to carry the A*24:02-B*39:01-DRB1*04:36 haplotype that had been deduced in the family study [Table 1]. There were also a number of other DRB1*04:36 associated probable HLA haplotypes deduced from these unrelated Taiwanese individuals

[Table 2]. Finally, we were able to further reveal that DRB1*04:36 is in association with DQB1*03:02 by the extended HLA-DQB1 typing of two members of the family study of the blood donors carrying DRB1*04:36.

DISCUSSION

In this study, we confirmed the DNA sequence of DRB1*04:36 is most likely to have been derived through a gene recombination event involving DRB1*04:03:01 and DRB1*11:01:01:01 in which DRB1*11:01:01:01 donated a fragment of its DNA sequence containing at least residue 291 to residue 308 to the recipient allele DRB1*04:03:01 [9]. Further, our population survey on HLA-DRB1 indicated that DRB1*04:36 is a low incidence allele in the Taiwanese population and it would seem to be completely absent from the mainland Chinese population. It can be observed that, from our results and those of Chu *et al.*, [9] DRB1*04:36 is closely linked in some individuals with B*39:01 at the HLA-B locus, while in some other individuals, DRB1*04:36 is not associated with B*39:01. Based on the study of the single family available to us, we were able to deduce the most probable HLA haplotype in association with DRB1*04:36 to be A*24:02-B*39:01-DRB1*04:36. This deduced probable DRB1*04:36 associated HLA haplotype is in fact one of the two DRB1*04:36 associated HLA haplotypes speculated on by Chu *et al.*, this deduction being based on one single individual's HLA typing [9]. Clearly, this indicates that a family study can provide a more precise approach to determine HLA allele associated HLA haplotypes and is a useful approach until a substantially large number of unrelated panel individuals are tested for the same purpose. We tested the HLA-DQB1 locus

DNA Pos.	110	120	130	140	150	160	170	180	190	200	
DRB1*04:03:01	<u>CACGTTTCTT</u>	<u>GGAGCAGGTT</u>	<u>AAACATGAGT</u>	<u>GTCATTTCTT</u>	<u>CAACGGGACG</u>	<u>GAGCGGGTGC</u>	<u>GGTTCCTGGA</u>	<u>CAGATACTTC</u>	<u>TATCACCAAG</u>	<u>AGGAGTACGT</u>	
DRB1*04:36	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	
DRB1*11:01:01:01	-----	-----T-CTC-	-----CGTC-----	-----	-----T-----	-----	-----	-----	-----	-----A-----	
DNA Pos.	210	220	230	240	250	260	270	280	290	300	
DRB1*04:03:01	<u>GCGCTTCGAC</u>	<u>AGCGACGTGG</u>	<u>GGGAGTACCG</u>	<u>GGCGGTGACG</u>	<u>GAGCTGGGGC</u>	<u>GGCCTGATGC</u>	<u>CGAGTACTGG</u>	<u>AACAGCCAGA</u>	<u>AGGACCTCCT</u>	<u>GGAGCAGAGG</u>	
DRB1*04:36	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	
DRB1*11:01:01:01	-----	-----	-----T-----	-----	-----	-----	-----A	-----G-----	-----T-----	-----AG-C-----	
DNA Pos.	310	320	330	340	350	360					
DRB1*04:03:01	<u>CGGGCCGAGG</u>	<u>TGGACACCTA</u>	<u>CTGCAGACAC</u>	<u>AACTACGGGG</u>	<u>TTGTGGAGAG</u>	<u>CTTCACAGTG</u>	<u>CAGCGGCGAG</u>				
DRB1*04:36	-----C-----	-----	-----	-----	-----	-----	-----				
DRB1*11:01:01:01	-----C-----	-----	-----	-----	-----	-----GT-----	-----				

Figure 1: In exon 2, the DNA sequence of DRB1*04:36 is identical to DRB1*04:03:01 except for a nucleotide segment from residue 286 to residue 308 (underlined) where DRB1*04:36 is the same as DRB1*11:01:01:01 (shaded). This observation suggests that DRB1*04:36 may be generated from a gene recombination event involving DRB1*04:03:01 and DRB1*11:01:01:01. Dashes indicate nucleotide identity with DRB1*04:03:01

AA Pos.	10	20	30	40	50	60	70	80	90	100
DRB1*04:03:01	<u>G</u>	<u>D</u>	<u>T</u>	<u>R</u>	<u>P</u>	<u>R</u>	<u>F</u>	<u>L</u>	<u>E</u>	<u>Q</u>
DRB1*04:36	*****	-----	-----	-----	-----	-----	-----F--D	-----A-----	-----	-----*****
DRB1*11:01:01:01	-----	-----Y	-----S	-----T	-----S	-----	-----N-----	-----	-----F-----	-----E-----

Figure 2: The amino acid sequence of DRB1*04:36 is identical to DRB1*04:03:01 (underlined), except for residues from position 67 to position 74. The amino acid fragment from position 67 to position 74 is the same as DRB1*11:01:01:01 (shaded). Dashes indicate amino acid identity with DRB1*04:03:01

Table 1: In the family study, it can be observed that the three siblings bear the DRB1*04:36 (underlined) allele and that DRB1*04:36 can be seen to be linked with A*24:02 (underlined) and B*39:01 (underlined) to form the haplotype A*24:02-B*39:01-DRB1*04:36 (shaded)

Donor ID	HLA-A*	HLA-A*	HLA-B*	HLA-B*	HLA-DRB1*	HLA-DRB1*	Deduced probable HLA haplotype associated with DRB1*04:36
AB3760	<u>24:02</u>	-	<u>39:01</u>	-	<u>04:36</u>	08:03	A*24:02-B*39:01-DRB1*04:36
AB3761	<u>24:02</u>	33:03	<u>39:01</u>	58:01	03:01	<u>04:36</u>	A*24:02-B*39:01-DRB1*04:36
AB3762 ^a	<u>24:02</u>	26:01	<u>39:01</u>	-	<u>04:36</u>	08:03	A*24:02-B*39:01-DRB1*04:36

^aStepsister. HLA=Human leukocyte antigen

Table 2: Deduced probable DRB1*04:36 associated HLA haplotypes based on the HLA typing of randomized unrelated Taiwanese donors and donors reported to the IMGT/HLA database [3]

Donor ID	HLA-A*	HLA-A*	HLA-B*	HLA-B*	HLA-DRB1*	HLA-DRB1*	Deduced probable DRB1*04:36 associated HLA haplotype
73171	11:01	11:02	15:02	27:04	04:05	04:36	A*11-B*27:04-DRB1*04:36 or A*11-B*27:04-DRB1*04:36
175375	24:02	31:01	35:01	40:01	04:36	15:01	A*24:02-B*40:01-DRB1*04:36
280942	24:02	33:03	46:01	58:01	04:05	04:36	A*24:02-B*46:01-DRB1*04:36
273412	02:XX	24:02	40:01	-	04:36	15:CNBA	A*24:02-B*40:01-DRB1*04:36
303924	11:01	24:02	27:04	40:01	04:36	14:XX	A*24:02-B*40-DRB1*04:36 or A*11-B*27-DRB1*04:36
318064	24:02	-	40:01	46:KP	04:36	09:MV	A*24:02-B*40:01-DRB1*04:36
289794	02:03	24:02	38:BD	40:01	04:36	15:XX	A*24-B*40-DRB1*04:36 or A*02:03-B*38-DRB1*04:36
323746	11:XX	11:XX	15:CAVN	46:XX	04:36	09:MV	A*11-B*15-DRB1*04:36
312559	11:XX	24:02	39:01	46:XX	04:36	09:MV	A*24:02-B*39:01-DRB1*04:36
317537	02:GFEX	24:02	38:AAGR	39:01	04:36	04:XX	A*24:02-B*39:01-DRB1*04:36 or A*02-B*38-DRB1*04:36
332921	02:XX	11:XX	27:04	46:GCIYM	04:36	08:03	A*11-B*27-DRB1*04:36
337764	11:JBCP	11:JCKA	27:KKKH	35:KUMP	04:36	15:01	A*11-B*27-DRB1*04:36
337747	11:JBCP	11:JCKA	27:KKKH	35:KUMP	04:36	15:01	A*11-B*27-DRB1*04:36
344934	24:02	-	40:01	54:BGMV	04:36	15:01	A*24:02-B*40:01-DRB1*04:36
358023	02:NNZG	24:02	40:01	46:XX	04:36	09:DAZX	A*24:02-B*40:01-DRB1*04:36
368754	02:XX	24:02	15:XX	40:01	04:36	09:01	A*24:02-B*40:01-DRB1*04:36
368702	24:02	31:01	40:01	-	04:36	14:54	A*24:02-B*40:01-DRB1*04:36
373830	24:02	-	39:01	40:XX	04:03	04:36	A*24:02-B*39:01-DRB1*04:36 or A*24:02-B*40-DRB1*04:36
395309	11:01	24:02	27:04	39:01	04:36	11:CTPB	A*24:02-B*39:01-DRB1*04:36 or A*11:01-B*27:04-DRB1*04:36
BN61 ^a	24:02	-	39:01	40:01	04:03	04:36	A*24:02-B*39:01-DRB1*04:36 or A*24:02-B*40:01-DRB1*04:36
175586 ^a	02	-	07	38	04:36	15:01:01	A*02-B*38-DRB1*04:36 or A*02-B*07-DRB1*04:36

^aDonors reported to the IMGT/HLA database [3]. When the HLA-A and HLA-B loci are taken into consideration, DRB1*04:36 is not strictly restricted to being associated with only one particular HLA-A or HLA-B allele. Only a few individuals display the A*24:02-B*39:01-DRB1*04:36 haplotype (shaded) observed in the family study and presented in Table 1. HLA=Human leukocyte antigen

in two of the three members of our single family, and these results revealed that DRB1*04:36 is linked with DQB1*03:02 in these persons.

Initially, DRB1*04:36 was first discovered in only one individual among 88 Bunun individuals who were studied and it was not detected in the other eight indigenous tribes of Taiwan (Atayal, Saisiat, Tsou, Rukai, Paiwan, Ami, Puyuma, and Yami); furthermore, it was also not

present when Ivatans from the Philippines and Minnan/Hakka from Taiwan were tested [15]. In the Allele Frequency Net Database (<http://www.allelefreqencies.net/>), DRB1*04:36 was not detected in 50, 614 USA National Marrow Donor Program Filipino individuals, 187 USA African American individuals, 1041 USA Caucasian individuals, 194 USA South Texas Hispanic individuals, 1305 individuals from the Netherlands, and

485 South Korea individuals. However, one individual from Libya and one individual from Chile were detected to be carrying DRB1*04:36 and these persons shared a common haplotype A*02-B*39-DRB1*04:36 (<http://www.allelefrequencies.net/>). In the present study, it was not detected among 29,721 individuals from mainland China. Among the 19 Taiwanese unrelated individuals who were found to be bearing DRB1*04:36, three individuals identified themselves as belonging to the Taiwanese indigenous Puyuma tribe, one individual identified himself as belonging to the Bunun tribe, and the remaining individuals indicated they had Minnan, Hakka, or Minnan and Hakka Southern Chinese ethnicity. This finding adds the Puyuma tribe from Taiwan to the Bunun tribe and there are now two indigenous tribes with DRB1*04:36 present among their members. If we consider the individuals who identified themselves to be Minnan, Hakka, or Minnan and Hakka, our findings seems to suggest that they are descendants from individuals who were involved in intermarriages between the Bunun/Puyuma Taiwanese indigenous tribes and the Minnan/Hakka ethnic groups, the latter having migrated to Taiwan from China.

According to Chu *et al.*, Taiwan's indigenous tribes, especially the East Coast tribes, are closely related to the Oceania and Australian indigenous peoples based on cultural and anthropological studies [15]. Further, high-frequency DRB1 alleles and HLA-A-B-DRB1 haplotypes found in Taiwan's indigenous tribes are also found in the Oceania and Australian indigenous peoples [15]. If we add the above findings to the fact that three persons from three different countries, namely, Australia, Chile, and Libya, have been shown to carry the very same DRB1*04:36 allele as some Taiwanese individuals as we have determined here, this suggests that a genetic association exist between these individuals.

Our family study clearly indicated that, in some incidences, the HLA haplotype in association with DRB1*04:36 is A*24:02-B*39:01-DRB1*04:36 without ambiguity. However, in the randomized Taiwanese population study, not all the participating individuals with DRB1*04:36 were found to have the same DRB1*04:36 associated haplotype. Several other DRB1*04:36 associated haplotypes may be deduced and these included: A*24-B*40-DRB1*04:36; A*11-B*27:04-DRB1*04:36; A*02:03-B*38-DRB1*04:36; A*11-B*15-DRB1*04:36; and A*24-B*39-DRB1*04:36. Incidentally, the haplotypes A*24-B*39-DRB1*04:36 and A*24-B*40-DRB1*04:36 are the two probable haplotypes speculated on by Chu *et al.* in their case study [9] and the haplotype A*02:03-B*38-DRB1*04:36 is one of the two probable haplotypes that may be deduced for the DRB1*04:36 bearing donor reported by

the Australian Laboratory [3]. We speculate therefore that, with further population studies, additional HLA haplotypes in association with DRB1*04:36 may be revealed in the future.

It is worth mentioning that the most direct and classic method to determine HLA haplotypes is through family studies if suitable test material from a number of key family members are available. Alternatively, a population study may be employed if a significant number of unrelated donors are available [5-7]. However, the haplotypes deduced through a population investigation are considered to be either likely or most probable. The significance of determining the ethnicity of individuals with DRB1*04:36 and its HLA linked haplotypes is that this information may now be employed in anthropological investigation of ethnicities. In addition, they will help search coordinators working at unrelated bone marrow donor registries with the allocation of appropriate unrelated bone marrow hematopoietic stem cell donors to patients who are in need of a transplant.

The number of known HLA alleles is increasing exponentially due to recent developments in DNA-based molecular typing technology [3]. The vast HLA diversity across ethnic groups is both unique and important. Facilitating an appropriate HLA-match for a given unrelated bone marrow stem cell donor allows successful stem cell transplantation to happen and relies on the accuracy of HLA typing. It also depends on having the spirit and strength to resolve the unknown, ambiguous, and low incidence genes that still are present in the HLA system.

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Conflicts of interest

There are no conflicts of interest.

Declaration of patient's consent

The authors certify that all the patients have obtained appropriate patient consent forms. In the form all patients have given their consents for their images and other clinical information to be reported in the journal. All

patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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