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Original Article

HLA haplotype in association with the low incidence C*07:66 allele found by case analysis of Taiwanese and mainland Chinese individuals

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ABSTRACT

Objectives: HLA-C*07:66 is a low-incidence HLA-C allele. The aim of the study is to report the Taiwanese and mainland Chinese ethnicities of individuals with C*07:66, together with its uniqueness and polymorphism.

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, 3, and 4 of the HLA-A, HLA-B, and HLA-C loci and exon 2 of the HLA-DRB1 and HLA-DQB1 loci using group-specific primer sets. The amplicons were sequenced in both directions using BigDye Terminator Cycle Sequencing Ready Reaction kit. The blood donors in this study consisted of randomized Taiwanese and mainland Chinese individuals and family members with the C*07:66 allele.

Results: The DNA sequence of C*07:66 is identical to that of C*07:02:01:01 for exons 2, 3, and 4, except for residue 688 in exon 4. This nucleotide substitution causes a single amino acid alteration to the protein sequence of C*07:02:01:01. Confirmation of the DNA and protein sequences of C*07:66 and the Taiwanese and mainland Chinese ethnicities of individuals with this allele were established in this study. One probable HLA C*07:66-associated HLA haplotype may be deduced from these individuals.

Conclusion: The information on the ethnicity of the C*07:66 allele and the deduced probable HLA haplotype associated with the low-incidence C*07:66 allele reported in this study may aid in HLA testing laboratories for reference purposes. In addition, they can be used by stem cell transplant donor search coordinators to help create, for patients bearing this uncommon HLA allele, strategies for finding compatible donors using bone marrow donor registries comprising unrelated individuals.

1. Introduction

New HLA alleles continue to be revealed and the recognition of HLA low-incidence alleles has enriched our understanding of the complexity of the HLA system. The major histocompatibility complex (MHC) in humans consists of several gene loci that are located on the short arm of chromosome 6 at 6p21.3. These loci are classified into MHC class I, class II, and class III regions. The genes encoding the HLA alleles are located in the MHC class I and class II regions. HLA genes are characterized by their extreme allelic polymorphism as well as their variations and diversity across different ethnic groups. HLA molecules have been definitively defined as transplant antigens and have a strong relevance when performing tissue transplantation. The molecular similarity of these molecules between donors and recipients is considered to be a predictive factor for graft survival and graft versus host disease. It is imperative to precisely characterize any unknown and low-incidence alleles encountered during routine HLA typing practice. To facilitate successful and comprehensive unrelated bone marrow hematopoietic stem cell donor search when patients are in need of hematopoietic stem cell transplantation, persistent efforts are needed to resolve unidentified, ambiguous, or low-incidence alleles to offer optimal HLA matching and donor selection.

Conflict of interest: none.

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The nucleotide sequence of HLA-C*07:66, which was initially detected in a Chinese individual with Han ethnicity, was first submitted to GenBank (accession number FJ629179) and the IMGT/HLA Database (submission number HWS10005968) in 2009, and the name HLA-C*07:66 was officially assigned by the World Health Organization HLA Nomenclature Committee [1]. A family study indicated that C*07:66 segregated as A*24:02- C*07:66-B*40:01-DRB1*12:02 haplotype [2]. Here we report the Taiwanese and mainland Chinese ethnicities of individuals bearing C*07:66 and the deduced probable HLA haplotypes found to be associated with C*07:66 based on HLA-A, HLA-B, HLA-C, and HLA-DRB1 alleles commonly shared across our randomized unrelated donors and family members with the C*07:66 allele. We further speculate that the deduced plausible HLA haplotypes associated with C*07:66 are restricted to individuals who are members of the Chinese or Taiwanese ethnic groups. In addition, through four family studies, we found that DRB1*12:02, present in the haplotype A*24:02-C*07:66-B*40:01-DRB1*12:02, is associated with DQB1*03:01.

2. Materials and Methods

Peripheral whole blood samples from a range of Taiwanese and Chinese ethnicity individuals were collected in acid citrate dextrose anticoagulant. A formal written consent was obtained from all the donors prior to blood collection. Whole blood samples with the anticoagulant 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-C, HLA-DRB1, and HLA-DQB1 loci using commercial polymerase chain reaction sequencing-based typing kits (Secore A/B/C/DRB1/DQB1 Locus Sequencing kits, Life Technologies, Brown Deer, WI, USA). High-resolution allelic sequencing was performed, as previously described [3–8]. Two sets of primer sequences were used. These were firstly B-CG: M13-BIN1-CGG (sense): TGTAAAACGACGGCCAGTCGGGGGCGCAGGACCCGG and P3′ exon 5B (anti-sense): GCTCCGATGACCACAACTGCT and secondly B-TA: M13-BIN1-TGA (sense): TGTAAAACGACGGCCAGTGGCGGGGGCGCAG-GACCTGA and P3′exon 5B (anti-sense): GCTCCGATGACCACAACTGCT. The amplicons were subsequently sequenced in both directions using a BigDye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems, Foster City, CA, USA) by following the manufacturer's instructions.

Determination of the deduced C*07:66-associated probable HLA haplotype in this study was performed by looking at the commonly shared HLA typing of the donors bearing C*07:66 across a sample of the randomized unrelated donors and family members. Where applicable, haplotype deduction based on HLA allelic homozygosity, as described previously, was employed [9,10].

3. Results

In this study, the oriental ethnicity of individuals with C*07:66 was identified. In addition, the study by Deng et al [2] is confirmed, which reported that the DNA sequence of C*07:66 is identical to that of C*07:02:01:01 in exons 2, 3, and 4 except for residue 688 (at codon 206; CTG->ATG) in exon 4 where cysteine (C) of C*07:02:01:01 is substituted by alanine (A) in C*07:66 (Fig. 1). This nucleotide replacement leads to an amino acid exchange wherein leucine (L) of C*07:02:01:01 is changed to methionine (M) in C*07:66 (Fig. 2).

```
exon                    80         90         100        110        120        130        140        150        160        170
C*07:02:01:01        GCTCCCA CTCCATGAGG TATTTCGACA CCGCCGTGTC CCGGCCCGGC CGCGGAGAGC CCCGCTTCAT CTCAGTGGGC TACGTGGACG ACACGCAGTT
C*07:66              ------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------

exon                   180        190        200        210        220        230        240        250        260        270
C*07:02:01:01     CGTGCGGTTC GACAGCGACG CCGCGAGTCC GAGAGGGGAG CCGCGGGCGC CGTGGGTGGA GCAGGAGGGG CCGGAGTATT GGGACCGGGA GACACAGAAG
C*07:66           ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------

exon                   280        290        300        310        320        330        340        350        360        370
C*07:02:01:01     TACAAGCGCC AGGCACAGGC TGACCGAGTG AGCCTGCGGA ACCTGCGCGG CTACTACAAC CAGAGCGAGG ACG|GGTCTCA CACCCTCCAG AGGATGTCTG
C*07:66           ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---|------- ---------- ----------

exon                   380        390        400        410        420        430        440        450        460        470
C*07:02:01:01     GCTGCGACCT GGGGCCCGAC GGGCGCCTCC TCCGCGGGTA TGACCAGTCC GCCTACGACG GCAAGGATTA CATCGCCCTG AACGAGGACC TGCGCTCCTG
C*07:66           ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------

exon                   480        490        500        510        520        530        540        550        560        570
C*07:02:01:01     GACCGCCGCG GACACCGCGG CTCAGATCAC CCAGCGCAAG TTGGAGGCGG CCCGTGCGGC GGAGCAGCTG AGAGCCTACC TGGAGGGCAC GTGCGTGGAG
C*07:66           ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------

exon                   580        590        600        610         620        630        640        650        660        670
C*07:02:01:01     TGGCTCCGCA GATACCTGGA GAACGGGAAG GAGACGCTGC AGCGCGCAG|A ACCCCCAAAG ACACACGTGA CCCACCACCC CCTCTCTGAC CATGAGGCCA
C*07:66           ---------- ---------- ---------- ---------- ---------|- ---------- ---------- ---------- ---------- ----------

exon                   680        690        700        710        720        730        740        750        760        770
C*07:02:01:01     CCCTGAGGTG CTGGGCCCTG GGCTTCTACC CTGCGGAGAT CACACTGACC TGGCAGCGGG ATGGGGAGGA CCAGACCCAG GACACCGAGC TTGTGGAGAC
C*07:66           ---------- -------A-- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------

exon                   780        790        800        810        820        830        840        850        860        870
C*07:02:01:01     CAGGCCAGCA GGAGATGGAA CCTTCCAGAA GTGGGCAGCT GTGGTGGTGC CTTCTGGACA AGAGCAGAGA TACACGTGCC ATATGCAGCA CGAGGGGCTG
C*07:66           ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------

exon                   880        890
C*07:02:01:01     CAAGAGCCCC TCACCCTGAG CTGGG
C*07:66           ---------- ---------- -----
```

Fig. 1. The DNA sequence of C*07:66 is identical to C*07:02:01:01 in exons 2, 3 and 4 except for residue 688 (at codon 206; underlined) in exon 4 where C of C*07:02:01:01 is substituted by A (shaded) in C*07:66. Exons 2, 3 and 4 are separated by pipes (|) between nucleotides 343 and 344 and 619 and 620 respectively. Dashes indicate nucleotide identity with C*07:02:01:01.

```
AA Pos.                10         20         30         40         50         60         70         80         90         100
C*07:02:01:01  CSHSMRYFDT AVSRPGRGEP RFISVGYVDD TQFVRFDSDA ASPRGEPRAP WVEQEGPEYW DRETQKYKRQ AQADRVSLRN LRGYYNQSED GSHTLQRMSG
C*07:66        ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------

AA Pos.                110        120        130        140        150        160        170        180        190        200
C*07:02:01:01  CDLGPDGRLL RGYDQSAYDG KDYIALNEDL RSWTAADTAA QITQRKLEAA RAAEQLRAYL EGTCVEWLRR YLENGKETLQ RAEPPKTHVT HHPLSDHEAT
C*07:66        ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------

AA Pos.                210        220        230        240        250        260        270        280        290        300
C*07:02:01:01  LRCWALGFYP AEITLTWQRD GEDQTQDTEL VETRPAGDGT FQKWAAVVVP SGQEQRYTCH MQHEGLQEPL TLSWEPSSQP TIPIMGIVAG LAVLVVLAVL
C*07:66        -----M---- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------

AA Pos.                310        320        330        340
C*07:02:01:01  GAVVTAMMCR RKSSGGKGGS CSQAACSNSA QGSDESLITC KA
C*07:66        ---------- ---------- ---------- ---------- --
```

Fig. 2. The nucleotide replacement, described in the Fig. 1, leads to the exchange of one amino acid at residue 206 where leucine (L) of C*07:02:01:01 is changed to methionine (M) (shaded) in C*07:66.

Table 1 shows a total of 30 unrelated and related individuals bearing C*07:66 obtained from Taiwan, mainland China, and the IMGT/HLA Database [1]. It can be observed that C*07:66 is almost always in association with B*40:01 in the HLA-B locus except for donor 7550800383 of the IMGT/HLA Database [1], which indicates that there is a strong linkage between the alleles C*07:66 and B*40:01. In the HLA-A locus, A*24:02 is found predominately to be associated with C*07:66, followed by A*02:07 and A*11:01, and then various other HLA-A alleles (Table 1). Similarly, in the HLA-DRB1 locus, DRB1*12:02 is the most frequently observed allele associated with C*07:66; however, many other HLA-A and DRB1 alleles also coexist with C*07:66. Based on the above observation, a probable C*07:66 association with an HLA-A/B/C/DRB1 haplotype may be deduced in the form of A*24:02-C*07:66-B*40:01-DRB1*12:02. This deduced probable C*07:66-associated haplotype is in fact identical to the C*07:66-associated haplotype reported in the family study conducted by Deng et al [2]. However, we are unable to deduce further probable HLA-A/B/DRB1 haplotypes that are in association with C*07:66 conclusively; this is because of the inconsistent presence of various alleles at the HLA-A and HLA-DRB1 loci. Table 2 shows the HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 typing of four family members with C*07:66 and of one of the C*07:66 positive donors reported to the IMGT/HLA Database as listed in Table 1. A commonly shared C*07:66-associated HLA haplotype with DQB1*03:01 may be deduced from these family members to be A*24:02-C*07:66-B*40:01-DRB1*12:02-DQB1*03:01. It is clear that the DRB1*12:02 allele within haplotype A*24:02-C*07:66-B*40:01-DRB1*12:02 is in linkage with DQB1*03:01.

4. Discussion

In this study, the Taiwanese and mainland Chinese ethnicities of individuals with C*07:66 was determined and confirmed. According to the Allele Frequency Net Database, C*07:66 has not been detected among the United States-based National Marrow Donor Program (NMDP) donors with African American, Asian Pacific Islander, Caucasian, Hispanic, or Native American ethnicities [11]. Therefore, the restriction of C*07:66 to Taiwanese and mainland Chinese populations indicates the ethnicity uniqueness of the allele. In other words, its conservation within individuals of Taiwanese and mainland Chinese descent is in contrast to many other HLA alleles, which are widely distributed across all races. The fact that C*07:66 has a tight association with B*40:01 further supports the unique nature of this allele and its specific characteristics.

From a panel of 29 individuals with C*07:66 (Cell 7550800383 excluded; Table 1), we deduced a probable C*07:66-associated HLA haplotype to be A*24:02- C*07:66-B*40:01-DRB1*12:02 based on the alleles shared in common by these individuals. However, when the alleles of HLA-A (A*24:02 excluded) and HLA-DRB1 loci (DRB1*12:02 excluded) of the individuals bearing C*07:66 are taken into consideration, C*07:66 does not seem to show strong linkage with any particular HLA-A or HLA-DRB1 loci allele (Table 1). In other words, a seemingly random genetic polymorphic combination of alleles from these loci co-exist with C*07:66. In addition, the polymorphic nature of C*07:66 is further demonstrated by Cell

Table 1
The deduced probable HLA-A, HLA-B, HLA-C, and HLA -DRB1 haplotypes in association with C*07:66 were determined based on the HLA typing of individuals who were either Taiwanese or mainland Chinese (cell number preceded with TB). The two cells (underlined) were reported to the IMGT/HLA Database. In all cases (except Cell 7550800383), C*07:66 can be seen to be linked consistently with B*40:01 (shaded). However, when the HLA-A and HLA-DRB1 alleles are considered, C*07:66 is not strictly associated with any particular HLA-A or HLA-DRB1 allele at the HLA-A and HLA-DRB1 loci, respectively. Only a few individuals carry the probable deduced HLA haplotype A*24:02-B*40:01-C*07:66-DRB1*12:02 (shaded). Interestingly, Cell 7550800383 carries C*07:66 without having an association with A*24:02 or DRB1*12:02.

Donor ID	HLA-A*		HLA-B*		HLA-C*		HLA-DRB1*	
105607	02:01	02:07	13:01	40:01	03:04	07:66	12:02	12:02
189303	02:07	24:02	40:01		03:04	07:66	12:02	15:01
227938	02:07	11:01	40:01	55:02	07:66	12:03	09:01	12:02
267106	24:02	33:03	40:01	58:01	03:02	07:66	03:01	12:02
280478	24:02	33:03	40:01	58:01	03:02	07:66	03:01	12:02
384041	24:02	33:03	40:01	51:01	07:66	14:02	09:01	12:02
376390	11:01	24:02	15:XX	40:01	07:66	08:01	09:CTZ	15:01
228659	02:03	24:02	38:02	40:01	07:02	07:66	04:10	16:02
TB10380	24:02	66:01	40:01	41:02	07:66	17:03	12:02	13:01
TB10602	02:01	24:02	40:01	40:01	04:03	07:66	12:02	15:01
TB02766	02:01	11:02	15:11	40:01	03:03	07:66	12:02	14:54
TB04740	02:07	24:02	40:01	46:01	01:02	07:66	04:05	09:01
TB06710	11:01	24:02	40:01	48:01	07:66	15:02	12:02	15:01
TB07554	02:64	24:02	15:18	40:01	07:04	07:66	04:01	12:02
TB09048	02:06	24:02	35:01	40:01	03:03	07:66	12:02	15:01
TB09049	11:01	24:02	39:15	40:01	07:66	15:02	12:02	12:02
TB00140	02:07	24:02	40:01	46:01	01:02	07:66	09:01	12:02
TB02350	24:02	24:02	40:01	40:06	07:66	08:01	08:03	12:02
TB02467	24:02	33:03	40:01	58:01	03:02	07:66	03:01	12:02
TB04142	02:01	11:01	40:01	48:01	07:66	15:02	12:02	15:01
TB04961	02:07	24:02	15:11	40:01	03:03	07:66	12:02	15:01
TB05020	24:02	26:01	15:02	40:01	07:66	08:01	12:02	12:02
TB05367	02:06	02:07	40:01	40:01	07:02	07:66	09:01	12:01
TB05921	24:02	33:03	40:01	58:01	03:02	07:66	03:01	12:02
TB05923	24:02	24:02	13:01	40:01	03:04	07:66	04:05	12:02
TB07316	01:01	24:02	15:17	40:01	07:01	07:66	12:02	13:02
TB07317	01:01	24:02	15:17	40:01	07:01	07:66	12:02	13:02
TB07318	24:02	24:02	40:01	40:01	03:04	07:66	12:02	16:02
SZBM02	11:01	24:02	07:02	40:01	07:66	07:67	01:01	12:02
7550800383	02:01	31:01	15:01	15:11	07:66	07:67	14:54	15:01

Table 2
The deduced HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 haplotype in association with C*07:66 was determined based on the HLA typing of the four family members with C*07:66 and a donor (SZBM02) with C*07:66 reported to the IMGT/HLA database. In all cases, C*07:66 can be seen to be linked consistently with A*24:02, B*40:01, DRB1*12:02 and DQB1*03:01 (shaded).

Relationship	Donor ID	HLA-A*		HLA-B*		HLA-C*		HLA-DRB1*		HLA-DQB1*	
Mother	TB06710	11:01	24:02	40:01	48:01	07:66	15:02	12:02	15:01	03:01	06:01
Son	TB07554	02:64	24:02	15:18	40:01	07:04	07:66	04:01	12:02	03:01	03:02
Sister	TB09048	02:06	24:02	35:01	40:01	03:03	07:66	12:02	15:01	03:01	06:02
Brother	TB09049	11:01	24:02	39:15	40:01	07:66	15:02	12:02	12:02	03:01	03:01
Father	TB02350	24:02	24:02	40:01	40:06	07:66	08:01	08:03	12:02	03:01	06:01
Father	TB05921	24:02	33:03	40:01	58:01	03:02	07:66	03:01	12:02	02:01	03:01
Son	TB05923	24:02	24:02	13:01	40:01	03:04	07:66	04:05	12:02	03:01	04:01
Brother	TB07316	01:01	24:02	15:17	40:01	07:01	07:66	12:02	13:02	03:01	06:04
Brother	TB07317	01:01	24:02	15:17	40:01	07:01	07:66	12:02	13:02	03:01	06:04
Sister	TB07318	24:02	24:02	40:01	40:01	03:04	07:66	12:02	16:02	03:01	06:02
—	SZBM02	11:01	24:02	07:02	40:01	07:66	07:67	01:01	12:02	03:01	05:01

7550800383 (Table 1), which shows neither an association with B*40:01 nor an association with A*24:02 at the HLA-A locus nor an association with DRB1*12:02 at the DRB1 locus. The extensive polymorphic nature of C*07:66 and its characteristic properties within the HLA genetic system are mysterious and need to be further investigated when additional individuals with C*07:66 are identified in the future.

Incidentally, the deduced probable C*07:66-associated HLA haplotype described above is exactly the same as the C*07:66-associated HLA haplotype identified by Deng et al [2] in a family study of a propositus bearing C*07:66. In Table 2, we further analyzed the HLA typing, including the HLA-DQB1 alleles, of four family members bearing C*07:66 and a C*07:66 donor reported to the IMGT/HLA Database. We observed that the commonly shared C*07:66 in association with HLA-A, HLA-B, HLA-C, and HLA-DRB1 haplotypes is exclusively associated with DQB1*03:01. This leads us to conclude that the DRB1*12:02 in the haplotype A*24:02-C*07:66-B*40:01-DRB1*12:02-DQB1*03:01 may exclusively link with DQB1*03:01 and that this haplotype is most probably restricted to oriental population individuals.

It is worth mentioning that the most direct and classic method to determine HLA haplotype is through a family study if test material from a number of key family members is available. Alternatively, a population study may be employed if a significant number of unrelated donors is available [4]. However, haplotypes deduced via a population investigation are generally considered to be likely or the most probable haplotypes.

The significance of determining the ethnicity of individuals with C*07:66 and its HLA-linked haplotypes is that this information may be employed in the anthropological investigation of races. Additionally, it allows search coordinators, using bone marrow donor registries made up of unrelated donors, to allocate appropriate unrelated bone marrow hematopoietic stem cell donors to their patients.

The number of known HLA alleles is increasing exponentially due to the recent development of DNA-based molecular typing technology. The outstanding diversity of HLA across ethnic groups is unique and important. Facilitating an appropriate HLA-match to an unrelated bone marrow stem cell donor helps to make stem cell transplantations successful, which depends on the accuracy of HLA typing. In turn, this requires the spirit and strength to resolve unknown, ambiguous, and low-incidence genes in the HLA system. Furthermore, the determination of haplotypes is essential when matching donor and recipient for unrelated stem cell transplantation since matching at the haplotype level has a better likelihood of matching at other loci within the HLA region than when donors are merely matched at the individual allele level.

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