Tzu Chi Medical Journal 2024; 36 (2): 166-174

Original Article

Association of HLA-C*07:359 with HLA-A, -B, and -DRB1 alleles in Taiwanese

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Abstract

Objectives: It is thought that Taiwanese indigenous people were the "first people" to populate Taiwan (Formosa) having been there for over 5000 years, preceding the Dutch colonization (from 1624 to 1662) and Spanish colonization (from 1626 to 1642). Taiwan's indigenes, represented by Austronesian language speakers, currently constitute approximately 2% of the total population in Taiwan. It is unknown whether they evolved from Taiwan's Paleolithic or Neolithic cultures, arrived during or after the Neolithic period from China or Southeast Asia or both. HLA studies on the Taiwanese indigenous population have found several intriguing genetic information showing one or two relatively frequently observed alleles and a small number of relatively less frequently observed ones. We report here a relatively frequently observed HLA-C*07:359 allele in the Taiwanese indigenous population, its linkage with HLA-B*39:01, and its probable associated HLA haplotype in two Taiwanese indigenous families. HLA-C*07:359 is a rarely observed allele in the HLA-C locus in the world populations. The objective of this study is to report the allele HLA-C*07:359 that is more frequently found in the Taiwanese population, especially in the Taiwanese indigenous people, to demonstrate that it has a close linkage with HLA-B*39:01 allele in the HLA-B locus and to show the plausible deduced HLA-A-C-B-DRB1-DQB1 haplotypes in association with HLA-C*07:359 in two families of Taiwanese indigenous unrelated individuals. **Materials and Methods:** The samples were peripheral whole blood, with dipotassium ethylenediaminetetraacetic acid and/or acid citrate dextrose anticoagulation additives. The sequence-based typing method was employed to confirm the low incidence of the allele of HLA-C*07:359 observed in Taiwanese. Polymerase chain reaction was carried out to amplify exons 2, 3, and 4 of the HLA-A,-B,-C,-DRB1 and-DQB1 loci with group-specific primer sets. Amplicons were sequenced using the BigDye Terminator Cycle Sequencing Ready Reaction Kit in both directions according to the manufacturer's protocol. **Results:** C*07:359 is an uncommon allele in the HLA-C locus in the world general population, according to our literature review. However, in this study, it is observed in the general Taiwanese population (frequency 0.41%), especially in the Taiwanese indigenous people at a frequency of 0.23%. In addition, we deduced two probable HLA haplotypes in association with C*07:359 in two indigenous families: A*24:02-C*07:359-B*39:01-DRB1*04:36 and A*24:02-C*07:359-B*39:01-DRB1*04:04. **Conclusion:** The two deduced HLA haplotypes associated with the uncommon C*07:359 allele that we report here are valuable for HLA tissue typing laboratories for reference purposes and for stem cell transplantation donor search coordinators to determine the likelihood of finding compatible donors in unrelated bone marrow donor registries for patients bearing the uncommon HLA allele. Since C*07:359 was found mostly in the Taiwanese indigenous population, we think the allele and its haplotypes we report here are important in population and anthropological studies.

Keywords: *HLA, Indigenous people, Sequence-based typing, Stem cell, Transplantation*

Submission : 21-Nov-2023
Revision : 03-Dec-2023
Acceptance : 26-Dec-2023
Web Publication : 26-Mar-2024

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Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_288_23

How to cite this article: Yang KL, Lin PY. Association of HLA-C*07:359 with HLA-A, -B, and -DRB1 alleles in Taiwanese. Tzu Chi Med J 2024;36(2):166-74.

Introduction

The HLA genetic system, situated within the human major histocompatibility complex (MHC) on the short arm of chromosome 6, is the most polymorphic genetic system known in man so far and its constituent genes encode cell surface products that play vital and critical roles in immune response for related and unrelated hematopoietic stem cell, solid organ, and tissue transplantations. HLA matching at the haplotype level minimizes the adverse effect on transplantation outcome, graft rejection, and graft-versus-host disease [1-3]. Hence, understanding the distribution of HLA alleles and haplotypes in different ethnic populations is crucial for transplant hospitals searching for an acceptable unrelated donor for hematopoietic stem cell or solid organ transplantation. Further, the gene products expressed by the HLA system are involved in the recognition of foreign antigen in association with HLA gene products that are referred to as restriction recognition [4]. It is a process that has evolved in a manner that enables the immune system in mammals to respond effectively to foreign antigens while at the same time to recognize but not respond to self-antigens [4]. Associations of HLA genes with autoimmune diseases, virus-related cancers, and infectious diseases have been reported [5,6]. It is noteworthy that recent researches have indicated HLA genotypes and related polymorphism can influence susceptibility, severity, and progression of coronavirus-19 disease [7-10]. In addition, HLA alleles are generally considered equidistant molecular units in population genetic and anthropological investigations [11].

The overall size of the MHC is about 4000 kb. Today, at least 37,500 different HLA Class I and II alleles have been reported. New and low-incidence HLA alleles are continually being discovered. Recognition of the novel and low-frequency alleles has enriched our appreciation of the complexity and the importance of the HLA system clinically and scientifically [12].

The population composition in Taiwan consists of Aborigines (indigenous peoples of Taiwan), Chinese Mainlanders, Hakka, Minnan, and other recent minor newcomers with Mainland Chinese and Southeast Asian ethnicities. Hakka and Minnan are descends of 17th-century immigrants from Guangdong and Fujian provinces of southeast China, whereas Chinese Mainlanders are immigrants from different provinces and territories of China after World War II [13].

The population of Taiwan's indigenes, officially classified into 16 tribes, represented by Austronesian language speakers about 800,000 people in number, if the indigenous peoples of the plains in Taiwan are included, that constitutes approximately 2% of the total population in Taiwan currently [14]. However, the actual number of the aborigines may be inaccurate since the government measurement follows the Aboriginal father's lineage. Therefore, if a child's father is Aboriginal and the mother is non-Aboriginal, the child is registered as an Aboriginal. However, if the child's father is non-Aboriginal and the mother is Aboriginal, the child is classified as non-Aboriginal. In the latter case, the descendants of these offspring must follow the government classification as non-Aboriginal [14]. Taiwanese Aborigines are Austronesian people. As such, their languages, different from the languages of Hakka, Mandarin, and Minnan, are similar to that of the peoples of the Philippines, Malay, Brunei, and other Polynesian ethnic groups [15]. The Dutch colonized Taiwan from 1624 to 1662 and Spain established a small colony of the Spanish Empire in the northern tip of Taiwan from 1626 to 1642 [Figure 1] [16,17]. Before the Dutch and Spanish colonization, the only inhabitants on the island were Taiwanese aborigines. They are thought to have been living in Taiwan for over 5000 years. The origin of Taiwan's aborigines remains mysterious. It is unknown whether they evolved from Taiwan's Paleolithic or Neolithic cultures, arrived during or after the Neolithic period from China or Southeast Asia or both, and whether individuals or groups came during a specific period or at various periods [18]. It was suggested that Taiwan's indigenous groups are more or less genetically related to both northern and southern Asians since certain HLA haplotypes found common to many indigenous tribes have also been observed in Inuit, Japanese, Maori, Mongolians, Papua New Guinea (PNG) Highlanders, Tibetans, and Thais [19]. Taiwan's indigenous peoples are highly homogeneous within each tribe but significantly different between tribes due to long-term isolation. The homogeneity of each tribe is evidenced by many HLA-A,-B, and-C alleles found to have the highest frequencies ever been reported in the world. For example, a high frequency of *HLA-A*24 (*86.3%) was found in one of the Taiwanese aboriginal Paiwan tribes [19], whereas *HLA-B*27* was found with a much higher prevalence among the Atayal Aborigines [20].

The DNA sequence of *C**07*:359* was first submitted to the IPD-IMGT/HLA Database in April 2014 by Anthony Nolan Research Institute, United Kingdom, without indication of the ethnicity of the donor and its HLA-associated haplotype [12]. A second confirmatory sequence of the *C**07*:359* was reported to the IPD-IMGT/HLA Database in July 2014 by us [12], Tzu Chi Immunogenetics Laboratory, Buddhist Tzu Chi Stem Cells Center, Hualien Tzu Chi Hospital, and Buddhist Tzu Chi Medical Foundation, Taiwan, and the donor in this case was a Taiwanese individual. However, no report of a *C**07*:359*-associated haplotype was indicated since the family study was impossible because of a lack of blood samples from the family members of the donor with this allele [12]. Since then, Tzu Chi Immunogenetics Laboratory continued to identify more individuals bearing this allele in the Taiwanese population [12]. Here, we report further information on the allele *HLA-C*07:359* as it appears to present more frequently in Taiwanese Aboriginal people.

Materials and methods

This retrospective study was conducted in accordance with the principles embodied in the Declaration of Helsinki. This study was exempted from our IRB. Formal written consent was individually given by the donors before blood collection when they enrolled in the Tzu Chi Bone Marrow Donor Registry initially. The samples were peripheral whole blood, with dipotassium ethylenediaminetetraacetic acid and/or acid citrate dextrose (ACD) anticoagulation additives. Peripheral whole blood samples from individuals with Aborigines,

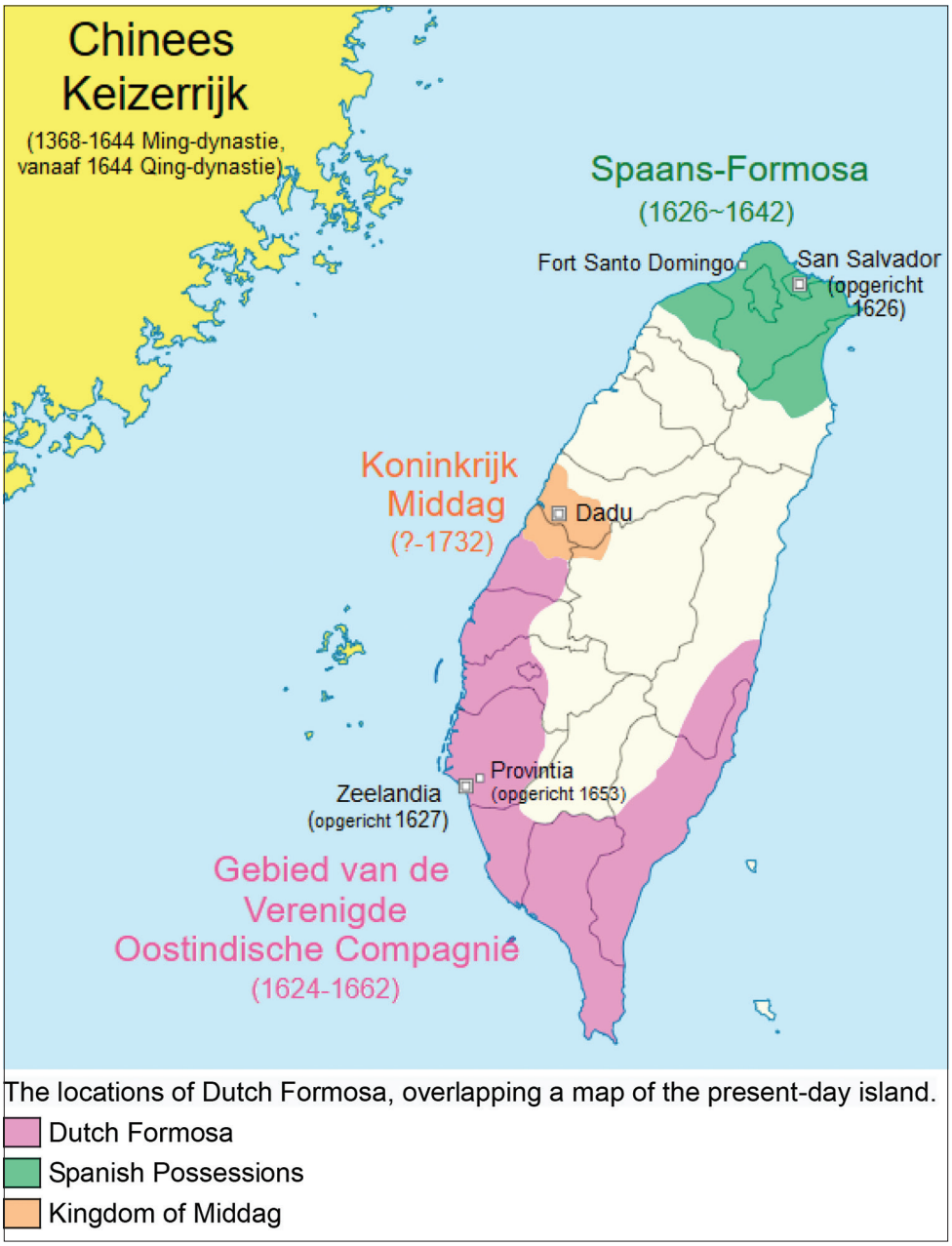

Figure 1: Colonization of Taiwan (Formosa) by Span and Dutch Empires in the year 1626–1642 and year 1624–1662 respectively

Chinese Mainlanders, Hakka, and Minnan ethnic groups were collected in vacutainers with ACD or EDTA anticoagulant. The whole blood samples were stored at −80°C until use. Peripheral blood total genomic DNA was extracted using QIAamp DNA Blood Mini kits according to the manufacturer's instructions (Qiagen, Hilden, Germany). The DNA obtained was subjected to HLA genotyping for the HLA-A, HLA-B, HLA-C, and HLA-DRB1, and in some cases, HLA-DQB1 loci using commercial polymerase chain reaction-sequencing-based typing kits (TBG, Medigen Biotechnology, Taipei, Taiwan). Sequencing products were preceded on the ABI 3730 DNA analyzer (Applied Biosystems, Foster City, California, USA). The sequences received were analyzed with AccuTYPE 7.2 analysis software.

Results

The DNA sequence of *C**07*:359* is identical to *C**07*:02:01:01* in exons 2, 3, and 4, except for codon 264 of exon 4, where GAG of *C**07*:02:01:01* is substituted by AAG in *C**07*:359* [Figure 2a]. The nucleotide substitution causes one amino acid replacement at residue 264, where glutamic acid (E) of *C**07*:02:01:01* is replaced by a lysine (K) in *C**07*:359* [Figure 2b].

From 2016 to 2020, a total of 9652 randomized general Taiwanese individuals, including 250 (2.59%) indigenous people, were tested for the presence of *HLA-C*07:359* allele. The probability of *HLA-C*07:359* being a Taiwanese Aboriginal ethnic tribes-related HLA-C locus allele is shown in Table 1. Among the 9,652 Taiwanese individuals,

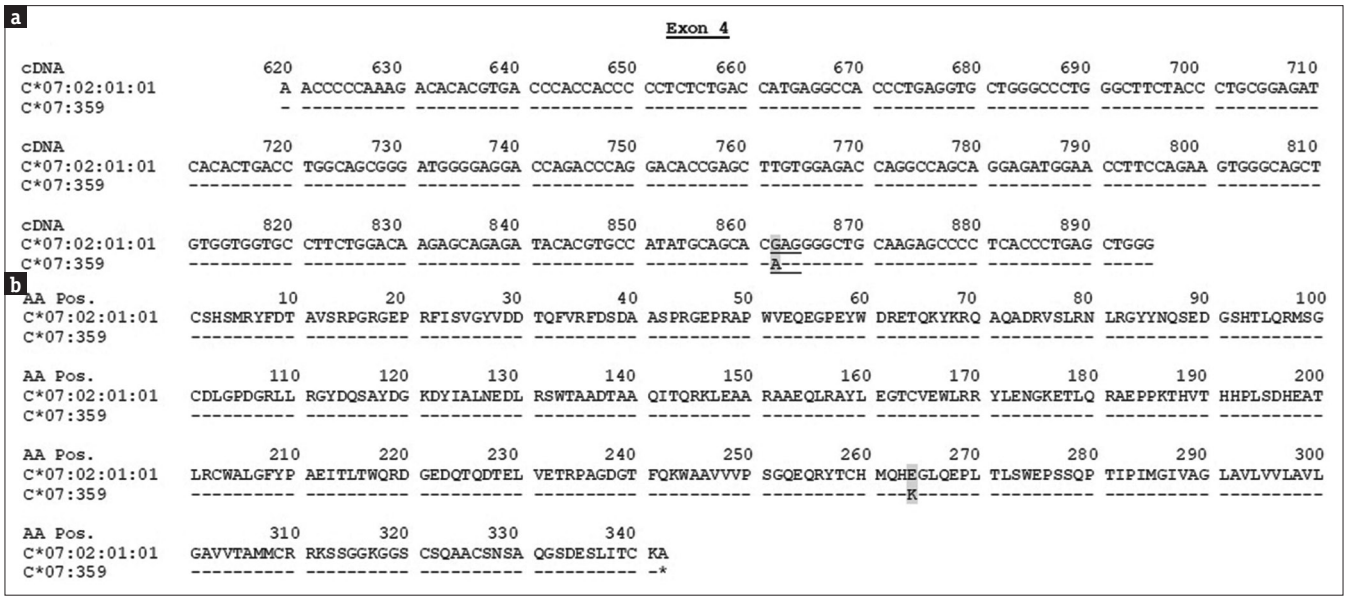

Figure 2: (a) The DNA sequence of *C*07:359* is identical to C*07:02:01:01 in exons 2, 3, and 4, except for nucleotide 862 (shaded) in codon 264 (underlined) of exon 4 (shown here), where G of *C*07:02:01:01* is substituted by an A in *C*07:359*. (b) The nucleotide substitution causes a single amino acid replacement at residue 264 where glutamic acid (E) of *C*07:02:01:01* is replaced by a lysine (K) in *C*07:359*. Dashes indicate nucleotide or amino acid identity with *C*07:02:01:01*

we found that 40 (0.41%) Taiwanese individuals carry *C**07*:359* alleles [Table 1]. As illustrated in Table 1, 22 out of the 40 Taiwanese individuals with *C**07*:359* claim to have an aboriginal ethnicity, rendering a frequency of 0.23% in Taiwanese Aboriginal people among the tested general Taiwanese population bearing *C**07*:359*. Eight out of the 40 (0.08%) individuals with *C**07*:359* indicate to have either Minnan or Hakka ancestral background, whereas ten of the 40 (0.10%) individuals with *C**07*:359* stated having no knowledge of their ancestral ethnicity information. However, we are not sure whether these two later groups of individuals with *C**07*:359* might, by any chance having maternal linkage to an aboriginal ancestry status since children whose aboriginal mother, grandmother, or great grandmother are not recognized as having the aboriginal status by the Taiwanese government. It follows, we conclude, the frequency of *C**07*:359* in the general Taiwanese population is 0.41%, of which 0.23% of the *C**07*:359* individuals are definitely with of Aboriginal ethnicity. This result suggests that *C**07*:359* is indeed an uncommon HLA-C locus allele in the Taiwanese population, and the allele is more likely to be detected in its indigenous population.

Table 1 shows 29 out of the 40 (72.5%) individuals with *C**07*:359* carry *B**39, of which 26 out of the 29 (89.7%) individuals with *B**39-bearing *B**39*:01*, suggesting that most of the *B**39 alleles associated with *C**07*:359* are in fact *B**39*:01*. This assumption is further supported by HLA typing of the siblings of two families [Table 2]. In Table 2 (family 1), extended HLA typing of the donors A3760 and A3761 is *A**24*:02*; *C**07*:02*, *07:359*; *B**39*:01*; *DRB1**04*:36*, *08:03:02* and *A**24*:02*, *33:03*; *C**03*:02*, *07:359*; *B**39*:01*, *58:01*; and *DRB1**03*:01*, *04:36*, respectively, which indicate that they share a common HLA haplotype: *A**24*:02-C*07:359-B*39:01-DRB1**04*:36*. Another piece of the evidence lending support to the association of *C**07*:359* and *B**39*:01* is two siblings of a second family [Table 2; Family 2] where donors A3586 and A3587 show that the two siblings share a common HLA haplotype: *A**33*:03-C*04:03-B*15:25-DRB1**12*:02*. By elimination, the donor A3586 carries a second HLA haplotype *A**24*:02-C*07:359-B*39:01-DRB1**04*:04* which in turn indicates the association of *C**07*:359* and *B**39*:01*. On the same issue, two unrelated indigenous individuals (donors A3760 and A6973) confirming the association of *C**07*:359* and *B**39*:01* is demonstrated in Table 3. However, Table 1 also shows that *C**07*:359* is in association with HLA-B alleles other than *B**39*:01* (i.e., *B**15*:11*, *B**15*:18*, *B**15*:25*, *B**38*:02*, *B**40*:01*, *B**40*:02*, *B**46*:01*, *B**48*:01/B*48*, *B**55*:02*, *B**56*:01/B*56,* or *B**67*:01*) suggesting that HLA-B allele in association with *C**07*:359* is not restricted to *B**39*:01* only.

In addition, Table 1 shows that in the HLA-A locus, 27 out of the 40 (67.5%) individuals with *C**07*:359* carry *HLA-A*24*, among which eight of them are *A**24 homozygous, indicating the probable association of *C**07*:359* and *A**24 in some *C**07*:359*-bearing individuals. Similarly, two of the 40 (5%) *C**07*:359* individuals (donors 3907 and 4699) are homozygous for *A**26*:01*, suggesting the associations of *C**07*:359* and *A**26*:01* in some individuals. In addition, we observed that 31 out of the 40 (77.5%) individuals with *C**07*:359* carry *DRB1**04* (*DRB1**04*:04* and *DRB1**04*:05* in majority) and two (5%) individuals (donors 3907 and 4699) are homozygous for *DRB1**08*:03*, indicating that the majority of DRB1 allele in association with *C**07*:359* is *DRB1**04* allele while in some individuals with *DRB1**08*:03* allele. However, other possible DRB1 alleles in association with *C**07*:359* include *DRB1**03*:01*, *DRB1**09*:01*, *DRB1**11*:01*, *DRB1**12*:01*, *DRB1**14*:54*, *DRB1**15*:01,* and *DRB1**16*:02* [Table 1]. Due to the low number of the *C**07*:359* individuals that were tested

Table 1: HLA typing of Taiwanese with C*07:359 (underlined)

Donor number	HLA										Ethnicity[#]
	A*		C*		B*		DRB1*		DQB1*		
7837	24:02	-	04:82	07:359	40:01	-	04:04	04:05	ND	ND	3[#]
9967	11:01	26:01	07:02	07:359	39:01	40:01	03:01	15:02	02:01	05:01	2[#], 3
5076	24:XX	-	01:02	07:359	39:XX	56:MS	04:04	15:BENG	ND	ND	?[#]
8119	11:02	26:01	07:359	12:02	40:02	67:01	11:01	14:54	ND	ND	1[#]
3413	11:XX	24:XX	03:04	07:359	39:XX	40:XX	04:ERKY	15:XX	ND	ND	1
8098	24:02	-	07:359	08:22	39:01	48:01	04:04	04:05	ND	ND	3
1422	11:02	26:01	07:359	12:02	40:02	67:01	11:01	14:54	ND	ND	1
1307	02:07	11:01	01:08	07:359	39:01	46:01	12:01	16:02	03:01	05:02	1
2763	24:XX	-	07:359	08:22	39:XX	48:XX	04:04	-	ND	ND	?
1109	02:03	26:01	07:02	07:359	38:02	67:01	14:54	16:02	05:02	-	1
7993	02:01	24:02	07:02	07:359	39:01	40:01	04:04	04:05	ND	ND	1
8265	11:02	24:02	07:02	07:359	39:01	40:01	04:04	04:05	ND	ND	?
1042	24:02	-	03:04	07:359	39:01	40:01	04:04	04:05	ND	ND	3
9904	02:01	24:02	03:03	07:359	39:01	55:02	04:04	04:05	ND	ND	3
5872	11:01	26:01	07:359	08:01	15:18	67:01	04:04	14:54	ND	ND	1
3907	26:01	-	07:02	07:359	39:01	67:01	08:03	-	ND	ND	1
7770	02:07	26:01	01:02	07:359	40:02	67:01	09:01	14:54	03:03	05:02	?
8444	02:01	24:02	07:359	08:01	39:01	55:02	04:04	14:05	03:02	05:03	?
1850	11:01	24:02	07:02	07:359	38:02	40:01	04:05	12:02	ND	ND	?
1851	02:03	24:02	07:02	07:359	38:02	39:01	04:04	15:02	03:02	05:01	?
3351	11:01	26:01	03:03	07:359	15:11	67:01	04:03	14:54	03:02	05:02	?
4182	11:01	24:02	07:02	07:359	38:02	40:01	04:05	12:02	ND	ND	?
4699	26:01	-	07:02	07:359	40:01	67:01	08:03	-	ND	ND	?
A3586	24:02	33:03	04:03	07:359	15:25	39:01	04:04	12:02	ND	ND	2, 3
A3737	02:01	34:01	01:02	07:359	39:01	56:01	04:04	15:02	ND	ND	3
A3760	24:02	-	07:02	07:359	39:01	-	08:03	04:36	ND	ND	3
A3761	24:02	33:03	03:02	07:359	39:01	58:01	03:01	04:36	ND	ND	3
A3780	02:01	34:01	01:02	07:359	39:01	56:01	ND	ND	ND	ND	3
A3773	24:02	-	07:359	08:22	39:01	48:01	04:04	-	ND	ND	3
A3774	24:02	-	07:359	08:22	39:01	48:01	04:04	-	ND	ND	3
A5161	11:01	24:02	07:02	07:359	38:02	40:01	04:05	12:02	ND	ND	3
A5162	02:06	24:02	07:02	07:359	39:01	40:01	04:05	08:03	ND	ND	3
A5517	24:02	34:01	01:02	07:359	39:01	56:01	04:04	15:02	ND	ND	3
A6001	11:01	24:02	04:03	07:359	15:25	39:01	04:04	16:02	ND	ND	3
A6005	02:01	24:02	04:82	07:359	39:01	40:01	04:04	04:05	ND	ND	3
A3741	02:01	34:01	01:02	07:359	39:01	56:01	04:04	15:02	ND	ND	3
A4977	24:02	-	07:359	08:01	39:01	48:01	04:04	12:02	ND	ND	3
A6973	11:02	24:02	07:02	07:359	39:01	-	04:04	04:05	03:02	04:01	3
A6891	11:02	24:02	07:359	08:01	15:02	39:01	04:04	15:02	03:02	05:01	3
A6574	24:02	-	04:82	07:359	39:01	40:01	04:05	-	03:02	-	3

Twenty-two out of 40 individuals carry C*07:359 are Taiwanese with indigenous ethnicity. [#]1=Minnan, 2=Hakka, 3=Indigenous people, ?=Unknown. ND: Not tested

Table 2: *C*07:359*-associated HLA haplotypes (underlined) observed in two family siblings bearing *C*07:359*

Donor number	HLA										Ethnicity
	A*		C*		B*		DRB1*		DQB1*		
A3760[#1]	24:02	-	07:02	07:359	39:01	-	04:36	08:03	ND	ND	3[Ω]
A3761[#1]	24:02	33:03	03:02	07:359	39:01	58:01	03:01	04:36	ND	ND	3
A3586[#2]	24:02	33:03	04:03	07:359	15:25	39:01	04:04	12:02	ND	ND	3
A3587[#2]	33:03	-	03:02	04:03	15:25	58:01	12:02	13:02	ND	ND	3

[#]Family, [Ω]Indigenous people. Donors A3760 and A3761 in Family 1 share a common haplotype *A*24:02-C*07:359-B*39:01-DRB1*04:36* (shaded). Donors A3586 and A3587 in Family 2 share a common haplotype *A*33:03-C*04:03-B*15:25-DRB1*12:02* (shaded). A second haplotype *A*24:02-C*07:359-B*39:01-DRB1*04:04* may be deduced in donor A3586 after eliminating the commonly shared haplotype. The haplotype *C*07:359-B*39:01* is therefore confirmed. ND: Not tested

for DQB1 locus, we were unable to identify a possible relationship between *C*07*:*359* and DQB1 alleles, except that we found a *C*07*:*359*-bearing individual (donor 1109) is homozygous for *DQB1*05*:*02* and another

Table 3: *C*07:359-B*39:01* haplotype (underlined) observed in two unrelated indigenous individuals

Donor number	HLA										Ethnicity
	A*		C*		B*		DRB1*		DQB1*		
A3760	24:02	-	07:02	07:359	39:01	-	04:36	08:03	ND	ND	3Ω
A6973	11:02	24:02	07:02	07:359	39:01	-	04:04	04:05	03:02	04:01	3

ΩIndigenous people, ND: Not tested

individual (donor A6574) is *DQB1**03*:02* homozygous, suggesting the association of *C**07*:359* with *DQB1**05*:02* and *DQB1**03*:02* occasionally. Other DQB1 alleles in association with *C**07*:359* may include *DQB1**02*:01* and *DQB1**05*:01* [Table 1]. Of particularly interesting is that four indigenous individuals (donors A3737, A3780, A5517, and A3741) with *C**07*:359* are found to carry the alleles of the HLA haplotype *A**34*:01-C*01:02-B*56:01* that were frequently observed in the Taiwanese indigenous Ami and Puyuma tribes, Maori, and PNG Highlanders [19]. Equally interesting are three (donors 7837, A6005, and A6574) of the 40 individuals with *C**07*:359* carry *C**04*:82,* and two individuals (donors A3760 and A3761) with *C**07*:359* carry *DRB1**04*:36* that are specifically found in Austronesian-speaking populations [21] and in Taiwanese indigenous subjects [22], respectively.

Discussion

The HLA system is an extremely polymorphic genetic system in human [12]. Analysis of distinctive HLA genes represents a valuable tool for anthropological investigation, population study [21-24], and in medical and clinical applications [1-3]. In Taiwan, today, there are 16 groups of officially recognized indigenous peoples, including Amis, Atayal, Bunun, Hla'alua, Kanakanavu, Kavalan, Paiwan, Puyuma, Rukai, Saisiyat, Tao, Tsou, Taroko, Sakizaya, Seediq, and Thao [14]. HLA studies on Taiwanese indigenous people have revealed several intriguing genetic information. For instance, *A**24*:20* was first found in the Atayal tribe of the Taiwan indigenous people [23], *DRB1**04*:36* was first discovered in an individual with Bunun Taiwanese aboriginal ethnicity [22], high frequency of *A**24 in Yami (52.1%) and Paiwan (86.3%) of Taiwanese indigenous people was also found to have a high frequency in PNG Highlanders and Micronesians, the most high-frequency DRB1 alleles, and some HLA-A-B-DRB1 haplotypes found in Taiwanese indigenous tribes are also detected in Oceania, Australian aborigines, south and northeast Asians and American Indians [23], and the most common haplotype of Trobriand Islanders *DRB1**08*:03:02-DQA1**01*:03-DQB1**06*:01* has frequently been found in Australian Aborigines from East and West Cape York and in Atayal Taiwanese Aboriginal population [24].

*C**07*:359* is an uncommon allele in HLA-C locus in the world's general population according to our literature review [Table 4]. However, in this study, it is observed in the general Taiwanese population (frequency 0.41%), especially in the Taiwanese indigenous people at a frequency of 0.23%. We revealed that over half of the Taiwanese individuals (n = 40) with *C**07*:359* allele are in the Taiwanese indigenous population (n = 22). This frequency of *C**07*:359* in Taiwanese indigenous people could increase had the Taiwanese government considered children with mother, grandmother, or great-great-grandmother having indigenous status recognized as an indigenous ethnic group.

To explore the incidence of *C**07*:359* allele in various populations or ethnic groups in various parts of the World, we looked up recent years (2019–2021) published studies on the bone marrow donor registries or cord blood banks in China, Germany, Italy, Japan, Saudi, Spain, and the United Kingdom, as well as European Federation for Immunogenetics and World Marrow Donor Association [25] [Table 4]. We did not find any case of the *C**07*:359* allele being reported in all the publications. For example, in the compiled catalog of common, intermediate, and well-documented HLA-A,-B, -C,-DRB1,-DRB3,-DRB5,-DQB1, and-DPB1 alleles from over 8 million individuals worldwide, data collected for 20 unrelated bone marrow hematopoietic stem cell donor registries and cord blood banks (which covered donors from African/African American, Asian/Pacific Islands, European/European descent, Middle East/North Coast of Africa, South or Central America/Hispanic/Latino, Native American, and unknown/not asked/multiple ancestries/ other) [25], and Hema-Quebec, Canada [26], in no case, *HLA-C*07:359* was reported. We assume the absence of *C**07*:359* allele in the over 8 million individuals of the 21 unrelated bone marrow donor registries and cord blood banks worldwide [25,26] may be attributed to the very few number of Taiwanese indigenous people were tested and coupled by its uncommon frequency status in the afford mentioned populations unlike as we have observed in the general Taiwanese population.

Among the indigenous individuals bearing *C**07*:359* in this study, several individuals indicate they belong to Amis, Bunun, or Puyuma tribes, and some gave no indication of their ancestor's tribe. It will be interesting to find out in future whether *C**07*:359* exists in the other officially recognized indigenous tribes in Taiwan.

Chu *et al*. reported the observation of *DRB1**04*:36* in a Bunun aboriginal individual in Taiwan and speculated the haplotype carrying *DRB1**04*:36* most likely could be *A**24*:02-B*39:01-DRB1**04*:36* or *A**24*:02-B*40:01-DRB1**04*:36* [22]. In this study, among the 22 aboriginal individuals with *C**07*:359*, two siblings [Tables 1 and 2; donors A3760 and A3761] with Puyuma indigenous background carry *DRB1**04*:36.* A commonly shared HLA-A-B-DRB1 haplotype, *A**24*:02-B*39:01-DRB1**04*:36*, can be deduced based on their HLA types [Table 2]. We, therefore, confirm, the speculation on one of the haplotypes proposed by Chu

Table 4: Number of people tested in world populations failed to find *C*07:359* allele

Populations studied	Number of individuals studied	References
European Federation for Immunogenetics	3,417,100	*HLA* 2017;89:104-113
China Marrow Donor Program	812,211	*HLA* 2018;92:199-205
ZKRD and DKMS registries	>5 millions	*HLA* 2018;92:206-214
Netherlands	1009	*HLA* 2019;93:474-483
Zhejiang Han Chinese	3548	*Intl J Immunologent* 2019;46:7-16
Saudi Stem Cells Donor Registry	2,405	*HLA* 2019;94:49-56
Italian Bone Marrow Registry	120,926	*HLA* 2019;94:285-295
Barcelona Cord Blood Bank	7972	*HLA* 2019;94:347-359
World Marrow Donor Association	>8 millions	*HLA* 2020;95:516-531
Japan Marrow Donor Program	177,041	*HLA* 2020;96:24-42
Rio de Janeiro, Brazil	1435	*HLA* 2020;96:268-276
German and Uzbek Minority, Kazakhstan	94	*HLA* 2020;96:615-620
Hubei Han Population, China	3732	Intl J Immunologent 2021;48:8-15
Anthony Nolan Register, United Kingdom		
African	5761	*HLA* 2021;97:15-29
Asian	37,505	
Bangladesh	1105	
BINME	599,410	
East Asian	4282	
African Caribbean	19,213	
India	10,597	
Jewish	9984	
Middle Eastern	1449	
Pakistan	3353	
Jeevan Stem Cell Foundation, India		
Malayalam speaking	356	*HLA* 2021;97:399-419
Telugu speaking	186	
Urdu speaking	397	
Kannada speaking	174	
Tamil speaking	7016	
Hema-Quebec Registry	3806	*HLA*2023;102:671-689 [26]

et al. [22]. In addition, we here reveal that *DRB1**04*:36* also exists in the Puyuma tribe in addition to the Bunun tribe of the Taiwanese indigenous people.

It is worth mentioning that among the 40 individuals with *C**07*:359* listed in Table 1, three individuals (Donors 7837, A6005, and A6574) were found to carry *C**04*:82* in addition to *C**07*:359*. The allele *C**04*:82* is a well-documented "rare" allele detected in Maori, Polynesian, and individuals from Pacific island nations such as Guam, Hawaii, Japan, Samoa, the Philippines, and Taiwan [21]. Donor 7837 even carries the same *A**24*:02-C*04:82-B*40:01* haplotype as the Maori/Polynesian donors [21]. The presence of *C**04*:82* in the three individuals with Taiwanese aboriginal ethnicity is in agreement with the suggestion made by Trejaut *et al*. that indigenous people in Taiwan and Polynesians share a common ancestral link [13].

Conclusions

In summary, our present work of *C**07*:359* found in the Taiwanese population reveals its distinctive presence in the general Taiwanese population, especially in Taiwanese indigenous people. The fact that *C**07*:359* was not detected in over 8 million individuals of the 21 unrelated bone marrow donor registries, and cord blood banks worldwide is intriguing. Future study for its presence in Austronesian language speakers in Micronesian, Polynesian, and Melanesian may shed some light on the distribution of this allele in Pacific islanders. Finally, the occupations of Taiwan (Formosa) by the Dutch and the Spanish in the 17th century left behind abundant assorted artifacts and remnants [Figure 3] [27,28]. As such, it is possible that there would be traces of Dutch and Spanish HLA genetic markers in the admixture of the Taiwanese nowadays gene pool. Therefore, the HLA study focuses on the pertaining topic may be worth of pursuing in future.

Data availability statement

Data are available on request from the authors.

Acknowledgments

The authors would like to offer special gratitude to the volunteer donors for their participation in our bone marrow donor registry and consent for scientific research. We would also like to thank Dharma Master Cheng Yen, founder of the Buddhist Compassion Relief Tzu Chi Foundation, for continuing support and kind encouragement both spiritually and intellectually. Furthermore, the generosity and camaraderie that our colleagues bestow on us are much appreciated.

Figure 3: Abundant assorted artifacts and remnants left behind after Dutch and Spanish occupations of Taiwan (Formosa) in the 17th century. (a) Renovated Spanish fort; (b) Remnant of Dutch castle; (c and d) Spanish old coins; (e) Dutch old coin

Financial support and sponsorship

Nil.

Conflict of interest

There are no conflicts of interest.

References

1. Nowak J, Nestorowicz K, Graczyk-Pol E, Mika-Witkowska R, Rogatko-Koros M, Jaskula E, et al. HLA-inferred extended haplotype disparity level is more relevant than the level of HLA mismatch alone for the patients survival and GvHD in T cell-replate hematopoietic stem cell transplantation from unrelated donor. Hum Immunol 2018;79:403-12.
2. Montgomery RA, Tatapudi VS, Leffell MS, Zachary AA. HLA in transplantation. Nat Rev Nephrol 2018;14:558-70.
3. Mayor NP, Hayhurst JD, Turner TR, Szydlo RM, Shaw BE, Bultitude WP, et al. Recipients receiving better HLA-matched hematopoietic cell transplantation grafts, uncovered by a novel HLA typing method, have superior survival: A retrospective study. Biol Blood Marrow Transplant 2019;25:443-50.
4. Charron D. HLA, immunogenetics, pharmacogenetics and personalized medicine. Vox Sang 2011;100:163-6.
5. Dendrou CA, Petersen J, Rossjohn J, Fugger L. HLA variation and disease. Nat Rev Immunol 2018;18:325-39.
6. Ghattaoraya GS, Dundar Y, González-Galarza FF, Maia MH, Santos EJ, da Silva AL, et al. A web resource for mining HLA associations with adverse drug reactions: HLA-ADR. Database (Oxford) 2016;2016:baw069.
7. Langton DJ, Bourke SC, Lie BA, Reiff G, Natu S, Darlay R, et al. The influence of HLA genotype on the severity of COVID-19 infection. HLA 2021;98:14-22.
8. Anzurez A, Naka I, Miki S, Nakayama-Hosoya K, Isshiki M, Watanabe Y, et al. Association of HLA-DRB1*09:01 with severe COVID-19. HLA 2021;98:37-42.
9. De Marco R, Faria TC, Mine KL, Cristelli M, Medina-Pestana JO, Tedesco-Silva H, et al. HLA-A homozygosis is associated with susceptibility to COVID-19. HLA 2021;98:122-31.
10. Migliorini F, Torsiello E, Spiezia F, Oliva F, Tingart M, Maffulli N. Association between HLA genotypes and COVID-19 susceptibility, severity and progression: A comprehensive review of the literature. Eur J Med Res 2021;26:84.
11. Buhler S, Sanchez-Mazas A. HLA DNA sequence variation among human populations: Molecular signatures of demographic and selective events. PLoS One 2011;6:e14643.
12. Barker DJ, Maccari G, Georgiou X, Cooper MA, Flicek P, Robinson J, et al. The IPD-IMGT/HLA database. Nucleic Acids Res 2023;51:D1053-60.
13. Trejaut JA, Kivisild T, Loo JH, Lee CL, He CL, Hsu CJ, et al. Traces of archaic mitochondrial lineages persist in Austronesian-speaking Formosan populations. PLoS Biol 2005;3:e247.
14. Available from: https://en.wikipedia.org/wiki/Taiwanese_indigenous_peoples. [Last accessed 2023 Nov 21].
15. Lai MJ, Wen SH, Lin YH, Shyr MH, Lin PY, Yang KL. Distributions of human leukocyte antigen-A, -B, and -DRB1 alleles and haplotypes based on 46,915 Taiwanese donors. Hum Immunol 2010;71:777-82.
16. Rubinstein MA. Taiwan: A new history. An east gate book. Armonk, New York, London England: M. E. Sharpe; 2007.
17. Available from: https://en.wikipedia.org/wiki/Dutch_Formosa. [Last accessed 2023 Nov 21].
18. Hill C, Soares P, Mormina M, Macaulay V, Clarke D, Blumbach PB, et al. A mitochondrial stratigraphy for Island Southeast Asia. Am J Hum Genet 2007;80:29-43.
19. Lin M, Chu CC, Lee HL, Chang SL, Ohashi J, Tokunaga K, et al. Heterogeneity of Taiwan's indigenous population: Possible relation to prehistoric Mongoloid dispersals. Tissue Antigens 2000;55:1-9.
20. Chou CT, Chen JM, Hsu CM, Chen SJ. HLA-B27 and its subtypes in 4 Taiwanese aborigine tribes: A comparison to Han Chinese patients with ankylosing spondylitis. J Rheumatol 2003;30:321-5.
21. Dunn PP, Lamb G, Selwyn C, Compton J, Yang E, Maiers M, et al. Diversity in exon 5 of HLA-C(*)04:01:01G is significant in anthropological studies. Hum Immunol 2016;77:426-8.
22. Chu CC, Lee HL, Lin M. Identification of a new HLA-DRB1 allele, HLA-DRB1*0436. Tissue Antigens 2004;63:279-81.
23. Scheltinga SA, Lai SM, van der Zwan AW, Tilanus MG, Wu S. A novel HLA-A24 (A*2420) allele identified in the Atayal tribe of Taiwan. Tissue Antigens 2000;55:65-7.
24. Chu CC, Lin M, Nakajima F, Lee HL, Chang SL, Juji T, et al. Diversity of HLA among Taiwan's indigenous tribes and the Ivatans in the

Philippines. Tissue Antigens 2001;58:9-18.

25. Hurley CK, Kempenich J, Wadsworth K, Sauter J, Hofmann JA, Schefzyk D, et al. Common, intermediate and well-documented HLA alleles in world populations: CIWD version 3.0.0. HLA 2020;95:516-31.
26. Lemieux W, Richard L, Nunes JM, Sanchez-Mazas A, Renaud C, Sapir-Pichhadze R, et al. A registry-based population study of the HLA in Québec, Canada. HLA 2023;102:671-89.
27. Spanish Remnants Found – Taipei Times. Available from: https://www.taipeitimes.com/News/taiwan/archives/2014/05/30/2003591592. [Last accessed 2023 Nov 21].
28. Research on Western Silver Coins Unearthed in Southern Taiwan. Available from: https://www.ith.sinica.edu.tw/quarterly_history_look.php?l=c&id=627. [Last accessed 2023 Nov 21].