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The degree of major histocompatibility complex matching between purebred Maltese and mongrel dogs using microsatellite markers

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ABSTRACT

Long-term maintenance of transplanted organs is one of the major factors that increases survival time of recipients. Although obtaining a major histocompatibility complex (MHC)-matched donor with the recipient is essential for successful organ transplantation, there have been limited reports on MHC matching between dogs. In this study, we analyzed the canine MHC matching rates using Maltese, one of the most popular purebred dogs, and mongrel dogs in Korea. Genomic DNA was extracted from blood leukocytes and DNA was amplified by polymerase chain reaction with primers specific to MHC microsatellite markers. The MHC matching degree was confirmed by the microsatellite markers using polyacrylamide gel electrophoresis. The MHC matching rates of each donor-recipient groups including Maltese-Maltese, mongrel-mongrel and Maltese-mongrel were 4.76%, 5.13% and 6.67%, respectively. There were no significant differences in the MHC matching degree between each group. These results demonstrate that MHC-matched donors could be selected from other breeds as much as from the same breed for transplantation. Knowledge of the MHC matching degree of purebred and mongrel dogs would offer valuable information not only for improving the success rate of organ transplantation surgery in canine patients but also for transplantation research using experimental canine models.

Keywords: Microsatellite markers; major histocompatibility complex; dogs

INTRODUCTION

Organ transplantation has become an accepted medical treatment for canine patients with end-stage organ failure [1-3]. However, survival after kidney transplantation in canine has been reported to be as low as 36% after 100-days, unlike in human clinical cases, wherein the 1-year patient survival rate is over 90% [2,4]. One of the major reasons leading to these unfavorable results in dogs might be insufficient pre-surgical tests that only screen for hyperacute rejection but not acute or chronic rejection caused by major histocompatibility complex (MHC) incompatibility [2,3,5,6]. Experimentally, the survival rate of canine kidney transplantation in MHC-identical or haploidentical groups was significantly higher, at more than 4 years, with immunosuppressants [7,8]. In general, the same canine breed is required as the organ transplant donor to prevent rejection. However, there is no data comparing

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Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization: Park KM; Data curation: Kwak HH; Formal analysis: Kwak HH; Funding acquisition: Woo HM; Investigation: Park KM, Kwak HH; Methodology: Park KM, Kwak HH; Project administration: Woo HM; Supervision: Park KM, Woo HM; Validation: Park KM, Woo HM; Writing - original draft: Kwak HH, Park KM; Writing - review & editing: Park KM.

MHC matching between different breeds. Therefore, such data would be beneficial for canine kidney transplantation.

Moreover, canines are widely used as one of the reliable preclinical, large-animal models for organ transplantation and immunological research [7,9]. Although small animal models, including mice and rat, incur lower costs to acquire and maintain, there are several limitations of using small animals in transplantation research [10,11]. Canines have strong similarities in surgical anatomy, physiology, and surgical techniques with humans and have contributed to the development of transplantation medicine fields [12,13].

Disparities in various polymorphic systems, mainly MHC, are the most important factors determining immunological rejection of transplants [14-16]. The canine MHC, or dog leukocyte antigen (DLA) complex, is poorly characterized, with only eight functional genes and five pseudogenes identified to date for the class I and II MHC gene region [17]. Furthermore, canine specific monoclonal antibodies for serological typing are not available and sequence-based typing methods of MHC alleles are time consuming [18]. Analysis of polymorphic microsatellites or short tandem repeats (STR) spanning the MHC provides an alternative method for rapid and accurate characterization of the region [19-21]. However, research on the canine microsatellite marker related to DLA have been limited to specific breeds [22].

The knowledge about MHC matching between different canine breeds would not only contribute to increasing the survival rate of transplantation in clinics but also would be helpful for studies using canine models. The aim of this study was to compare the diversity of MHC matching from purebred and mixed breed dogs using highly polymorphic microsatellite markers.

MATERIALS AND METHODS

Sample collection and DNA extraction

A total of 28 canine blood samples, which have the DEA 1.1 positive blood type, were obtained from the veterinary medical teaching hospital in Korea in micro EDTA tubes and stored at −20°C until DNA isolation. The samples were composed of two canine species, including 15 Malteses and 13 mongrels. DNA was isolated from leukocytes using the DNA extraction kit (Intron, Sungnam, Korea). The concentration of the DNA samples was measured using a spectrophotometer (Nanodrop 2000c; Thermo Scientific, Waltham, MA, USA).

Polymerase chain reaction (PCR) and DNA electrophoresis

The primer sequences of microsatellite markers of DLA class I and II, FH2200 and FH2202, are listed in **Table 1**, according to previous reports. PCR was performed using PCR master mix (2X TOPsample™ DyeMIX; Enzynomics, Daejon, Korea) with genomic DNA, specific primers, and distilled water. PCR amplification was performed using the T Professional standard 96 gradient machine (Biometra, Goettingen, Germany) with the following conditions: denaturation at 94°C for 3 min, followed by 39 cycles at 94°C for 30 sec, 59°C for 45 sec and 72 °C for 30 sec. A final extension step was followed at 72°C for 10 min. Trisacetate-EDTA polyacrylamide gel (4.5%) electrophoresis was used to detect the PCR products. PCR products were loaded into wells using electrophoresis equipment (EPS 2A200; Amersham Biosciences, Little Chalfont, UK) for 5 h (FH200) and 3 h 50 min (FH2202) under

100 voltage. One or 2 bands of DLA were shown by autoradiography with UV light (Gbox EF2; Syngene, Cambridge, UK).

DLA microsatellite analysis

The visualized bands of MHC class I or II of each dog were designated by alphabet letters according to their band size, as described previously (**Supplementary Figs. 1** and **2**) [22,23]. We assigned the results into 3 groups according to the matching degree; full-match, haplo-match, and unmatched groups. Donor-recipient pairs were divided into 3 groups; Maltese-Maltese, mongrel-mongrel, and Maltese-mongrel.

Statistical analysis

Fisher's exact test was used for statistical analysis. Difference was considered significant at $p < 0.05$.

RESULTS

A total of 105, 78, and 195 donor-recipient pairs were used, comprising Maltese-Maltese, mongrel-mongrel, and Maltese-mongrel dogs, respectively. The percentage of MHC class I matching from Maltese-Maltese, mongrel-mongrel, and Maltese-mongrel are shown in **Table 2**. The degree of MHC class I full-match was 8.57%, haplo-match was 10.48%, and unmatched was 80.95% in the Maltese-Maltese pair. The degree of MHC class I full-match was 0%, MHC class I haplo-match was 21.79%, and MHC class I unmatched was 78.21% in the Maltese-mongrel pair. The degree of MHC class I full-match was 3.59%, MHC class I haplo-match was 16.41%, and MHC class I unmatched was 80.00% in the mongrel-mongrel pair. The results do not show significant differences in MHC class I matching from each donor-recipient pair group.

The percentage of MHC class II matching from Maltese-Maltese, mongrel-mongrel, and Maltese-mongrel are shown in **Table 3**. The degree of MHC class II full match was 0.95%, haplo-match was 19.05%, and unmatched was 80.00% of in the Maltese-Maltese pair. The degree of MHC class II full-match was 0%, haplo-match was 21.79%, and unmatched was

Table 1. The sequence of primer of DLA microsatellite marker

Primer		Sequence
MHC class I		
FH2200	Forward	5′-GGCATGATCGTGGAGTCCC-3′
	Reverse	5′-CCCACCCCAGTTGTCCTATT-3′
MHC class II		
FH2202	Forward	5′-GTTGAGTGGTTGCCTTTAGC-3′
	Reverse	5′-CAGGATCTTCATATGTCACC-3′

DLA, dog leukocyte antigen; MHC, major histocompatibility complex.

Table 2. The degree of MHC class I in donor-recipient pairs from Maltese and mongrel dogs

Group*	No. of full match pairs (%)	No. of haplo-match pairs (%)	No. of nonmatch pairs (%)	Total
Maltese-Maltese	9 (8.57)	11 (10.48)	85 (80.95)	105 (100.00)
Mongrel-Mongrel	0 (0)	17 (21.79)	61 (78.21)	78 (100.00)
Maltese-Mongrel	7 (3.59)	32 (16.41)	156 (80.00)	195 (100.00)
Maltese-Mongrel	7 (3.59)	32 (16.41)	156 (80.00)	195 (100.00)

There were no significant differences between all groups ($p > 0.05$).
MHC, major histocompatibility complex.
*Pair of donor-recipient.

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Table 3. The degree of MHC class II in donor-recipient pairs from Maltese and mongrel dogs

Group*	No. of full match pairs (%)	No. of haplo-match pairs (%)	No. of nonmatch pairs (%)	Total (%)
Maltese-Maltese	1 (0.95)	20 (19.05)	84 (80.00)	105 (100.00)
Mongrel-Mongrel	0 (0)	17 (21.79)	61 (78.21)	78 (100.00)
Maltese-Mongrel	5 (2.56)	49 (25.13)	141 (72.31)	195 (100.00)

There were no significant differences between all groups ($p > 0.05$).
MHC, major histocompatibility complex.
*Pair of donor-recipient.

Table 4. The degree of MHC matching in donor-recipient pairs from Maltese and mongrel dogs

Group*	No. of suitable pair (%)				No. of non-suitable pair (%)				
	M†-M‡	M-H	H-M	H-H	M-U	U-M	H-U	U-H	U-U
Maltese-Maltese (n=105)	0 (0)	2 (1.90)	0 (0)	3 (2.86)	8 (7.62)	1 (0.95)	7 (6.67)	14 (13.33)	70 (66.67)
		5 (4.76)					100 (95.24)		
Mongrel-Mongrel (n=78)	0 (0)	0 (0)	0 (0)	3 (3.85)	0 (0)	0 (0)	13 (16.67)	13 (16.67)	48 (61.54)
		4 (5.13)					74 (94.87)		
Maltese-Mongrel (n=195)	0 (0)	1 (0.51)	2 (1.03)	10 (5.13)	6 (3.08)	3 (1.54)	19 (9.74)	37 (18.97)	117 (60.87)
		13 (6.67)					182 (93.33)		

There were no significant differences between all groups ($p > 0.05$).
MHC, major histocompatibility complex; M, full match; H, haplo-match; U, nonmatch.
*Pair of donor-recipient, †MHC class I, and ‡MHC class II.

78.21% in the Maltese-mongrel pair. The degree of MHC class II full-match was 2.56%, haplo-match was 25.13%, and unmatched was 80.00% in the mongrel-mongrel pair. The results did not show significant differences in MHC class II matching from each donor-recipient pair group.

Overall, the degree of MHC matching in class I and class II from Maltese-Maltese, mongrel-mongrel, and Maltese-mongrel are shown in **Table 4**. The number of MHC matching pairs were 5 (4.76%), 4 (5.13%), and 13 (6.67%) in Maltese-Maltese, mongrel-mongrel, and Maltese- mongrel groups, respectively. The results do not show significant differences in MHC matching from each donor-recipient pair group.

DISCUSSION

Microsatellites or STRs are di-, tri-, or tetra nucleotide repeats showing sufficient length variation in the alleles [2,24]. Two polymorphic microsatellite markers, tetranucleotide repeats of $(GAAA)_n$ or $(GATA)_n$, have been reported in dogs; one is C.2200, which is located in the MHC class I region near DLA-53, and the other one is C.2202, which is located in the MHC class II region near DLA-DRB2 [25].

Analysis of MHC matching between different canine breeds is necessary because it is difficult to find blood-related organ donors in companion dogs compared to that in humans. In addition, dogs have a higher transplant failure rate than human and feline recipients because of less effective immunosuppressants to control rejection; however, the reasons are not well-defined yet. Although kidney transplantation has usually been performed without MHC matching in feline patients due to difficulties in obtaining a transplantable organ from blood related donors similar to dogs, post-op prognosis is better than canine recipients [2,26]. Based on previous literature, the median survival time of kidney transplant recipients from unrelated donors have ranged from 360 to 613 days in feline [26]. In contrast, a previous report shows that the median survival time after kidney transplant was 24 days in canine recipients from unrelated donors [2].

Non-MHC proteins derived from different canine breeds could also induce chronic rejection [27]. However, studies on kidney transplantation using MHC-matched mongrel dogs have shown that the post-op survival rate was much higher than that with MHC-unmatched dogs, indicating that these non-MHC factors are controllable by the administration of immunosuppressants [2,8]. Similarly, as organ transplantation across racial groups have been overcome in humans, genetic differences due to race disparity between donors and recipients is not considered a major factor—in contrast to MHC matching [28,29].

Recently, ABO-incompatible organ transplantation has been widely used in human transplants by desensitization using plasmapheresis, immunoglobulins, B cell depletion via CD-20 antibodies and inhibition of complement activation [30,31]. Although rejection may be induced by different blood type antigens, these desensitization techniques have rarely been used in dogs. Moreover, human antibodies have proven ineffective in dogs [32,33]. Fortunately, most dogs have the same universal blood type, which is DEA1.1 positive [34]; therefore, obtaining canine donors and recipients with matching blood types is not a major constraint, as in human transplantation.

STR genotyping is a useful method for pre-operative selection for transplantation, not only in humans but also in dogs [8,35]. Similarly, in humans, the degree of STR disparities between donor and recipient are associated with postoperative survival time, and moreover, severity of graft-versus-host disease (GvHD) [36]. Therefore, knowledge of the degree of MHC matching is essential for successful results in organ transplantation.

Using the same breed of dog as the donor has been commonly considered for allogenic transplantation to reduce post-op organ rejection. In the present study, we compared the degree of MHC matching between Maltese, purebred, and mongrel dogs. The results showed that percentage of suitable pairs, which are identical or haplo-identical matching, were 4.76% in Maltese-Maltese, 5.13% in mongrel-mongrel, and 6.67% in Maltese-mongrel with no significant differences. The rate of selection of suitable individuals for allogenic transplantation among the possible canine donors would not be very different between the same and different breeds. These results suggest that dogs of the same breed are not necessary for acquiring matching organ donors.

In human, the probability of two randomly selected unrelated individuals are of matching type is very low and varies from race to race. According to a previous report, the probability of HLA matching are 1/11,000 for white American–white American, 1/98,000 for African American–African American, 1/113,000 for African American–white American, 1/29,000 for Asian American–Asian American, and 1/223,000 for Asian American–White American, respectively [37]. In order to increases the probability, worldwide database through the organ transplantation center and marrow donor programs have been used. As results, now, approximately 75–90% of white American and 16–60% of African American patients have the possibilities to find HLA matched donor from unrelated individuals [37,38]. However, even if HLA matched pair using cellular assays of compatibility, only 9.4% of donor-recipient pair were matched for all alleles of DRB1, DQ and DP in MHC class II using DNA-based identification [39]. Therefore, methods are being developed to successfully transplant from HLA unmatched and unrelated donor, as mentioned earlier. In this study, MHC matching probability was relatively high between unrelated 2 dogs compared to previous human reports. This may have been due to the possibilities that dog have relatively less DLA disparity or we used different experimental approaches using microsatellite markers as compared previous studies using serological or DNA-

based methods. In the future, active organ transplantation would be possible if organ donation program and cell bank systems of the companion animals are established.

There were a few limitations in the present study. First, only one breed, Maltese, was included in this experiment as the purebred group. Hence, additional purebred groups might be added for future studies. Furthermore, collecting samples from dogs from various regions and countries will be required to improve the reliability of the experimental results.

Despite MHC-matched transplantation, many animal and human patients have suffered from chronic rejection and diverse complications of immunosuppressants. Infection, malignances, nephrotoxicity, hypertension, gingival overgrowth, diabetes mellitus have been reported as complications of post-transplant immunosuppression, which deteriorates the quality of life for recipients [2,5]. In order to improve the quality of life, development of new immunosuppressants or techniques with fewer side effects would be necessary. Recently, studies on organ transplantation without immune rejection using transplant tolerance created through mixed chimerism and patients-specific artificial organs developed using autologous stem cells have been reported [8,40]. These might lead to optimistic improvement in rejection-free organ transplantation without the use of immunosuppressants in the future.

In conclusion, the present study is the first to compare the degree of DLA matching between purebred Maltese and mongrel dogs. Any breed of canine can be considered as organ donors. Our findings would be beneficial not only for veterinary clinical field but also for medical research using canine models.

SUPPLEMENTARY MATERIALS

Supplementary Fig. 1

Polyacrylamide gel electrophoresis of amplified MHC class I microsatellite marker. All of the dogs have 1 or 2 bands which were shown in Maltese (A) and mongrel (B) dogs. The location of their bands was equal or different from each other. Each band was labeled by alphabet latter according to size. All bands were located between 500 and 600 bp.

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Supplementary Fig. 2

Polyacrylamide gel electrophoresis of amplified MHC class II microsatellite marker. All of the dogs have 1 or 2 bands which were shown in Maltese (A) and mongrel (B) dogs. The location of their bands was equal or different from each other. Each band was labeled by alphabet latter according to size. All bands were located between 400 and 500 bp.

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