Asian-Aust. J. Anim. Sci.
Vol. 22, No. 8 : 1078 - 1084
August 2009

www.ajas.info

Melanocyte-stimulating Hormone Receptor (MC1R) Genotype and Its Effects on Coat Color in Korean Jindo Dogs

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ABSTRACT : The Jindo dog is a Korean natural monument and is recognized by the Federation Cynologique Internationale. A prominent feature is the diverse coat color within the breed. To analyze the genetic basis of variation in the Jindo coat color, we sequenced the protein-coding regions of the melanocortin 1 receptor gene (MC1R). The MC1R coding sequence was determined from 154 dogs in five breeds (Jindo, Labrador Retriever, English Springer Spaniel, Belgian Malinois, and German Shepherd). To confirm the genetic structure of sampled populations, we tested for Hardy-Weinberg equilibrium (HWE) and computed F_{st}. The sample populations did not significantly deviate from HWE. F_{st} was 0.02 between white and fawn Jindo dogs; this was lower than F_{st} between breeds. Six single nucleotide polymorphisms (SNPs) were detected in the MC1R coding region. Among the six SNPs, five were non-synonymous (S90G, T105A, Q159P, M264V, and R306ter) and one was synonymous SNP (Y298Y). From the SNPs, we predicted four haplotypes (H1, H2, H3, and H4) for Jindo MC1R. Jindo dogs had different haplotypes corresponding to different coat colors. H1 was frequently observed in white Jindo dogs with an odds ratio of 5.03 (95% CI: 2.27-11.18, $p<0.0001$), whereas H2 and H4 were observed only in fawn Jindo dogs. Our findings indicate that SNP haplotype can influence coat color. Knowledge of MC1R haplotypes can help discriminate white and fawn coats in Jindo dogs. We hope this report will trigger more research into the genetics of this traditional Korean dog and will be a reference for dogs of Asian origin. Also, our results will provide a useful genetic marker for Jindo dog breeders who have selected for specific colors. (**Key Words** : Melanocortin 1 Receptor Gene, Korean Jindo Dog, Single Nucleotide Polymorphisms, Microsatellite Markers, Coat Color)

INTRODUCTION

Jindo, a county in South Korea (Figure 1a), consists of islands covering 430.6 km^2 and is home to 41,184 people. Approximately 13,000 dogs of the Jindo breed live in the county based on a survey conducted by the Jindo County Office (http://tour.jindo.go.kr/english/index.htm). The Jindo dog is a Korean natural monument and has been protected by law since 1962. In 2004, the Korean Jindo dog was recognized by the Fédération Cynologique Internationale (FCI) as an original valid standard and classified into Group 5 Spitz primitive types, Section 5 Asian Spitz and related breeds (http://www.fciconnect.com).

Research on the Jindo dog began in the late 1960s and was reviewed by Lee at al. (2000). Diverse coat colors have been reported in Jindo dogs, including fawn, white, black, red, and brindle (Mori, 1940; Lee and Kim, 1993). Among the diverse coat colors, fawn and white are most popular and are preferentially selected by pet owners (Figure 1b and c). We investigated the genetic basis of coat-color variation in Korean Jindo dogs.

Whether canine follicular melanocytes synthesize red/yellow pheomelanin or black/brown eumelanin is determined by a small set of genes. Among the candidate genes for dog coat-color variation (Schmutz and Berryere, 2007), the melanocortin 1 receptor gene (*MC1R*), which is located on chromosome 5 (Schmutz et al., 2001), is a candidate gene that influences coat color (Everts et al., 2000; Newton et al., 2000). *MC1R* corresponds to an extension locus (E; Little, 1957), and three alleles ($E/E^M/e$)

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Received October 30, 2008; Accepted April 2, 2009

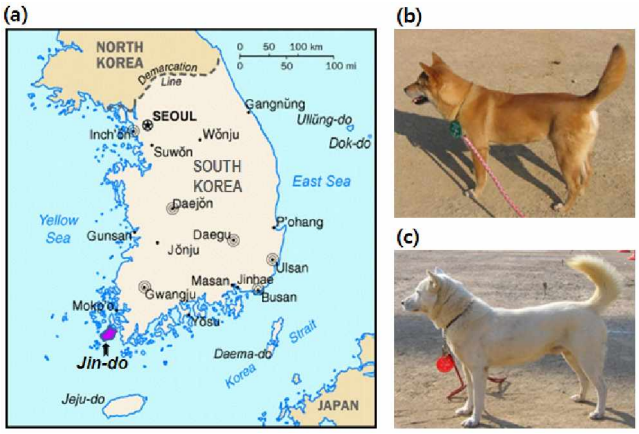

Figure 1. (a) Map of Jindo County. Korean Jindo dogs with fawn (b) and white (c) coats.

have been reported. The E allele corresponds to the wild-type *MC1R*, and the phenotype is black/brown or red/yellow. The E^M and e alleles are caused by single nucleotide polymorphisms (SNPs) in individuals with a melanistic mask and pheomelanic coat color, respectively (Newton et al., 2000; Schmutz et al., 2002, 2003). Therefore, we surveyed *MC1R* to understand coat-color variation in the Jindo dog.

MATERIALS AND METHODS

Animals

Genomic DNA samples were extracted from blood or buccal mucous membrane of 154 dogs: 57 Korean Jindo (JD) from the Korean Jindo and Domestic Animals Center, Jindo County, Korea; 17 Belgian Malinois (BM) and 36 German Shepherd (GSD) from the National Institute of Health, Korea Center for Disease Control and Prevention, Seoul, Korea; and 35 Labrador Retriever (LR) and nine English Springer Spaniel (ESS) from Samsung Everland Inc., Yongin, Gyeonggi, Korea.

Microsatellite markers

Eight unlinked microsatellite markers (FH2010, FH2054, PEZ01, PEZ03, PEZ05, PEZ08, PEZ10, and PEZ15) reported by Neff et al. (1999) were used for the analysis of population genetic structure (Table 1). The 10 μl PCR reaction contained 10 ng of DNA, 0.3 μM of each primer, 0.5 U of Top-*Taq*™ DNA Polymerase, 10× buffer (CoreBioSystem, Seoul, Korea), and 200 μM dNTPs. After an initial incubation at 94°C for 5 min, PCR was performed for 36 cycles consisting of 94°C for 30 s, a variable annealing temperature (52°C for PEZ03, 55°C for PEZ05, 58°C for PEZ10, 59°C for PEZ08 and PEZ15, and 62°C for PEZ01, FH2010, and FH2054) for 50 s, and 72°C for 1 min, followed by a final extension at 72°C for 10 min. Genotyping was carried out using fluorescently-labeled primers of FAM, HEX, and TET on an ABI 310 DNA Sequencer (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions. The length of the PCR product was determined using Genotyper version 2.5 (Applied Biosystems).

MC1R sequencing

To sequence the full-length *MC1R* coding region, we designed primers from *MC1R* genomic sequences, NC_006955.2. The forward primer (JdMF), 5'-AAG ACA CCT GAG AGC GAG GA-3', was designed from -52 to -32 bp upstream of the *MC1R* translation start codon, and the reverse primer (JdMR), 5'-ATC CAC CAC ACC ACA GAT CA-3', was from +95 to +115 bp downstream of the *MC1R* stop codon. The 25 μl PCR reaction contained 20 ng of DNA, 0.6 μM of each primer, 1 U of Top-*Taq*™ DNA Polymerase, 10×buffer (CoreBioSystem), and 400 μM dNTPs. After an initial incubation at 94°C for 5 min, PCR was performed for 35 cycles consisting of 94°C for 30 s, 62°C for 1 min, and 72°C 1 min, followed by a final extension at 72°C for 5 min. PCR products were confirmed by 2% agarose gel electrophoresis and were purified with 96-well PCR Cleanup Filter Plates, MultiScreen HTS™ PCR (Millipore, Seoul, Korea). Sequences were determined with an ABI 3730 DNA Analyzer (Applied Biosystems) according to the manufacturer's instructions. The sequencing results were analyzed with BioEdit version 7.0.9.0 (Hall, 1999). The protein sequences of all predicted haplotypes were aligned with human (GenBank accession number X65634), mouse (X65635) and fox (X90844) MC1R sequences.

Statistical analysis

Allele diversity (expected heterozygosity, H_e) was calculated with the following formula: $H_e = 2n\times(1-\Sigma q^2)/(2n-1)$ (Nei and Roychoudhury, 1974). A Hardy-Weinberg equilibrium (HWE) test and *F* statistics were computed in GenePop (version 4.0). Expected haplotypes and associations were determined in Hapanalyzer version 1.0 (http://hap.ngri.go.kr/). The JD individuals were divided into two coat color groups, white and fawn. After that, we calculated the expected odds ratio for dogs with white coats.

RESULTS

Genetic structure of sample populations

The microsatellite markers are described in Table 1. Most of the markers were polymorphic in all breeds used in this study, except for the ESS, in which *PEZ15* failed to amplify, and BM, in which *PEZ05* was monomorphic. Allele diversity did not differ from that reported by Neff et

Table 1. Genetic structure of the sampled populations based on eight microsatellite markers

Marker	Name Repeat type Chr.	FH2010 tetra cfa24	FH2054 tetra cfa12	PEZ01 di cfa7	PEZ03 tetra cfa19	PEZ05 tetra cfa12	PEZ08 tetra cfa17	PEZ10 tetra cfa14	PEZ15 tetra cfa5	Average heterozygosity[e]
Neff et al.[a]	Alleles	220-247	138-185	095-133	095-153	096-121	213-260	282-302	200-245	-
	Allele *n*	11	13	9	18	7	16	4	10.0	
	H_e	0.52	0.94	0.55	0.79	0.67	0.73	0.86	0.81	
JD[b]	Alleles	226-242	146-174	107-131	108-138	96-112	227-255	280-324	204-250	0.7913
	Allele *n*	5	8	7	10	5	7	11	9.0	
	H_e[c]	0.686	0.804	0.815	0.861	0.739	0.790	0.868	0.778	
	p-value[d]	0.057	0.099	0.003	0.360	0.976	0.159	0.029	0.437	
White JD[b]	Alleles	226-242	146-174	107-127	114-138	96-112	227-247	280-324	204-250	-
	Allele *n*	5	8	6	8	5	5	9	8	
	H_e[c]	0.764	0.821	0.807	0.886	0.714	0.786	0.864	0.836	
	p-value[d]	0.015	0.081	0.086	0.837	0.699	0.093	0.403	0.604	
Fawn JD[b]	Alleles	230-242	150-174	107-131	114-135	96-108	227-255	284-312	204-224	-
	Allele *n*	4	7	7	8	4	6	8	5.0	
	H_e[c]	0.614	0.807	0.764	0.807	0.757	0.821	0.843	0.714	
	p-value[d]	0.372	0.886	0.241	0.336	0.728	0.650	0.027	0.837	
LR[b]	Alleles	230-242	146-166	115-131	117-138	92-112	227-243	280-296	208-238	0.6726
	Allele *n*	4	5	5	7	5	5	7	5.0	
	H_e[c]	0.518	0.527	0.627	0.841	0.651	0.725	0.789	0.696	
	p-value[d]	0.214	0.869	0.776	0.015	0.372	0.218	0.001	0.050	
ESS[b]	Alleles	226-242	146-170	115-123	111-144	104-112	223-243	284-304		0.7347
	Allele *n*	5	6	3	7	3	3	3		
	H_e[c]	0.748	0.795	0.672	0.836	0.571	0.571	0.714		
	p-value[d]	0.166	0.121	0.097	0.647	0.788	0.788	1.000		
BM[b]	Alleles	226-238	146-178	111-119	114-135	100	223-247	272-296	200-216	0.6143
	Allele *n*	3	6	3	7	1	6	7	4.0	
	H_e[c]	0.534	0.752	0.590	0.750	0.000	0.727	0.766	0.708	
	p-value	0.097	0.205	0.866	0.418		1.000	0.290	0.149	
GSD[b]	Alleles	226-238	150-166	111-123	120-132	100-112	227-247	268-304	208-242	0.5717
	Allele *n*	4	5	4	5	3	5	9	5.0	
	H_e[c]	0.595	0.726	0.535	0.634	0.227	0.611	0.805	0.500	
	p-value	0.382	0.491	0.576	0.404	1.000	0.517	0.425	0.416	

[a] Published marker information (Neff et al., 1999).
[b] Breed name abbreviations: JD = Jindo; LR = Labrador Retriever; ESS = English Springer Spaniel; BM = Belgian Malinois; GSD= German Shepherd.
[c] H_e: Unbiased expected heterozygosity (Nei and Roychoudhury, 1974).
[d] Hardy-Weinberg equilibrium test p-value computed in GenePop (version 4.0).
[e] Average heterozygosity for eight MS markers in each breed examined.

al. (1999). Because the LR, ESS, BM, and GSD are maintained for special purposes, we examined Hardy-Weinberg Equilibrium (HWE). Higher heterozygosity was observed in JD than in other breeds. Most of the markers indicated that the sample populations did not significantly deviate from HWE. Average heterozygosity (mean value) for eight MS markers in each breed examined was calculated in Table 1.

Pair-wise comparisons of F_{st} (Wright, 1965) are shown in Table 2. JD had lower F_{st} values than other breeds, and LR and ESS had high F_{st} compared to BM and GSD. These results indicate that JD is a more ancestral type in which a wide range of alleles are maintained. Indeed, LR and ESS are bred for special purposes such as drug detecting or serving as guide dogs, and BM and GSD are bred as military working dogs. To improve the physical abilities of dogs, LR, ESS, BM, and GSD individuals are frequently introduced from outside the breeding population. Therefore, this difference in F_{st} may be linked not only to breed differences, but also to working ability. JD covered the allele ranges of the other breeds, indicating that they could also be used for work purposes.

Table 2. Genetic differences (F_{st}) between pairs of breeds[a] for the eight microsatellite markers

Breed 1	Breed 2	FH2010	FH2054	PEZ01	PEZ03	PEZ05	PEZ08	PEZ10	PEZ15	All loci
White JD	Fawn JD	0.03	-0.03	0.07	0.02	0.02	0.00	0.07	0.02	0.02
JD	LR	0.10	0.05	0.22	0.02	0.18	0.01	0.11	0.00	0.07
	ESS	0.06	0.12	0.04	0.07	0.20	0.22	0.01		0.12
	BM	0.15	0.12	0.12	0.10	0.40	0.12	0.06	0.04	0.15
	GSD	0.27	0.11	0.12	0.11	0.30	0.07	0.10	0.06	0.14
LR	ESS	0.12	0.11	0.11	0.07	-0.02	0.25	0.12		0.13
	BM	0.12	0.26	0.27	0.05	0.64	0.14	0.12	0.03	0.23
	GSD	0.33	0.19	0.21	0.11	0.53	0.05	0.13	0.20	0.24
ESS	BM	0.03	0.06	0.07	0.12	0.75	0.29	0.14		0.24
	GSD	0.10	0.09	0.06	0.16	0.62	0.34	0.12		0.27
BM	GSD	0.25	0.17	0.03	0.07	0.07	0.28	0.16	0.14	0.20

[a] Breed name abbreviations: JD = Jindo; LR = Labrador Retriever; ESS = English Springer Spaniel; BM = Belgian Malinois; GSD = German Shepherd.

MC1R allele frequency

In total, six SNPs were detected. Allele frequencies and expected heterozygosity are shown in Table 3. Korean JD had five SNPs, and we predicted four MC1R haplotypes. The protein sequences of haplotypes are aligned and illustrated in Figure 2.

MC1R haplotype prediction

From the six SNPs, we predicted four *MC1R* haplotypes to be present in over 5% of JD individuals. The haplotype

Table 3. Observed allele number and frequency in each breed[a] for the six SNPs, with expected heterozygosity

Position A.A	Position SNP	Observed allele number						Observed allele frequency					
		White JD	Fawn JD	LR	ESS	BM	GSD	White JD	Fawn JD	LR	ESS	BM	GSD
								Expected heterozygosity (H_e)					
90	286												
S	A	39	21	54	3	32	71	0.75	0.34	0.77	0.17	0.94	0.99
G	G	13	41	16	15	2	1	0.25	0.66	0.23	0.83	0.06	0.01
								0.38	0.45	0.36	0.29	0.11	0.03
105	286												
A	G	52	30	55	3	32	72	1.00	0.48	0.79	0.17	0.94	1.00
T	A	0	32	15	15	2	0	0.00	0.52	0.21	0.83	0.06	0.00
								0.00	0.5	0.34	0.29	0.11	0.00
159	470												
P	C	13	33	16	3	33	72	0.25	0.53	0.23	0.17	0.97	1.00
Q	A	39	29	54	15	1	0	0.75	0.47	0.77	0.83	0.03	0.00
								0.38	0.5	0.36	0.29	0.06	0.00
264	799												
M	A	52	62	70	18	0	0	1.00	1.00	1.00	1.00	0.00	0.00
V	G	0	0	0	0	34	72	0.00	0.00	0.00	0.00	1.00	1.00
								0.00	0.00	0.00	0.00	0.00	0.00
298	894												
Y	C	38	58	70	18	34	72	0.73	0.94	1.00	1.00	1.00	1.00
Y	T	14	4	0	0	0	0	0.27	0.06	0.00	0.00	0.00	0.00
								0.4	0.12	0.00	0.00	0.00	0.00
306	916												
R	C	2	40	1	18	33	72	0.04	0.65	0.01	1.00	0.97	1.00
ter	T	50	22	69	0	1	0	0.96	0.35	0.99	0.00	0.03	0.00
								0.07	0.46	0.03	0.00	0.06	0.00
Total		52	62	70	18	34	72						

[a] Breed name abbreviations: JD = Jindo; LR = Labrador Retriever; ESS = English Springer Spaniel; BM = Belgian Malinois; GSD = German Shepherd.

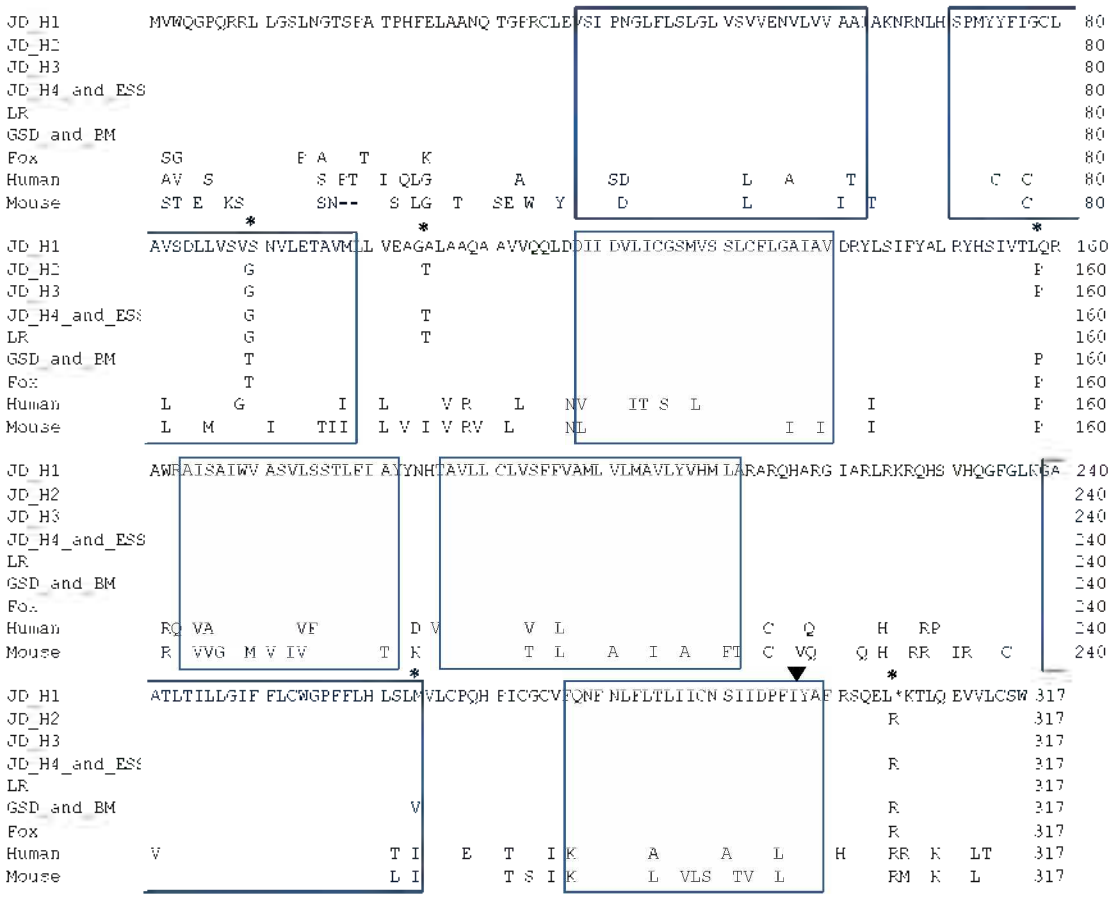

Figure 2. Protein-coding sequence of dog *MC1R* and a comparison to those of other mammals. Amino acid sequences of each breed haplotype were inferred from genomic DNA compared to sequences for Arctic fox (GenBank accession number X90844), human (X67594), and mouse (X65635). Differences from the Jindo H1 haplotype are indicated at the appropriate residue; dashes indicate insertions that maximize similarity. Putative transmembrane helices are boxed (Newton et al., 2000); asterisks mark non-synonymous SNP sites (S90G, T105A, Q159P, M264V, and R306ter); an arrowhead marks the synonymous SNP site (Y298Y).

association test is shown in Table 4. The H1 haplotype was frequently observed in white JD, with an odds ratio of 5.03 (95% CI: 2.27-11.18, p<0.0001), whereas H2 and H4 haplotypes were observed only in fawn JD. Because F_{st} was 0.02 between white and fawn JD (Table 2), and this was lower than F_{st} values between breeds, these results might not have been caused by population isolation between white and fawn dogs.

Table 4. Haplotype association test between white and fawn JDs

Genotype	Haplotype			
	H1	H2	H3	H4
	AGAACT	GACACC	GGCATT	GAAACC
White JD				
Homozygote	12	0	1	0
Heterozygote	11	0	7	0
Lacking the haplotype	3	26	18	26
Fawn JD				
Homozygote	0	4	1	1
Heterozygote	18	16	2	6
Absent the haplotype	13	11	28	24
Odds ratio (95% CI) to be White JD	5.03(2.27-11.18)	0.00(N/A)	3.03(0.88-10.51)	0.00(N/A)
Chi-Square	15.15	23.22	2.31	5.37
p-value	0.0001	0	0.1285	0.0075

DISCUSSION

Among the six SNPs, A286G was located in the 5' region and replaced the 90th position serine with glycine (S90G). The S allele was more frequently observed in white JD, LR, BM, and GSD, but the G allele was more frequently observed in fawn JD and ESS. MC1R is a seven-transmembrane G-protein coupled receptor (GPCR), and S90G is located in the second transmembrane domain. An S or T at this position is evolutionarily conserved; SNPs at similar positions are gain-of-function mutations, including E94K or L99P in other vertebrates (Newton et al., 2000). White and fawn JD had different allele frequency distributions, implying that S90G is a major factor in JD coat-color variation.

The next SNP position was A313G, in which the 105th position threonine was replaced with alanine (T105A). Only fawn JD were not biased at this position. ESS were biased toward the T allele, but other breeds were biased toward the A allele. White JD and GSD were fixed for the A allele. The A allele is conserved in the human and fox, but differs in the mouse. Newton et al. (2000) assumed that this SNP has no effect on protein function. Our results support Newton's assumption, because a high frequency of the T allele was observed in fawn JD and ESS, which do not have a homologous coat color pattern.

The third SNP was C470A; the proline at the 159th position was replaced with glutamine (P159Q). Again, fawn JD were not biased at this position. White JD, LR, and ESS were biased toward the Q allele, but BM and GSD were mostly fixed for the P allele. The P residue is conserved in other mammals, but varies among dog breeds. Although Newton et al. (2000) reported that P159Q is a neutral mutation because of a Q residue in chicken, we think differences between P and Q in polarity and solubility might influence receptor function.

The fourth SNP was A789G; the methionine at the 264th position was replaced with valine (M264V). The V allele was fixed in BM and GSD, but all other breeds only had the M allele. The M allele residue is conserved in the fox, but not in the human and mouse. The V allele causes a melanistic mask, which shows as a black mask in breeds such as GSD, Great Dane, and Pug (Schmutz et al., 2003). We also found the V allele in BM, which has a melanistic mask. This result indicates the close relationship between BM and other breeds.

The fifth SNP is the synonymous T894C. This SNP was observed only in white and fawn JD (Y298Y). The T allele was present at a low frequency in fawn JD, but in 25% of white JD. Because this SNP does not cause an amino acid change, it may be neutral and may have no phenotypic effects.

The last SNP, C916T, replaced the 306th position arginine with a premature termination codon (R306ter). Both alleles were frequently observed in fawn JD, but most individuals were heterozygous. Interestingly, the ter allele was predominant in white JD, and only two white JD individuals were heterozygous. Additionally, LR was fixed for the ter allele. However, the other breeds predominantly had the R allele. The R residue is conserved in other mammals. The T allele is associated with a yellow coat in LR and is present in a wide range of dog breeds (Newton et al., 2000; Schmutz et al., 2002), but previous reports did not test for it in white-coated individuals. In our study, white JD were almost fixed for the ter allele, and no homozygotes were observed in fawn JD. Berryere et al. (2005) reported that two amino acid changes, A82S and R83H, result in most fawn coats. Because fawn JD had a normal *MC1R* genotype, we assume dominant agouti functioning. Our findings indicate that not only SNPs, but also SNP haplotypes influence dog coat color. Knowledge of MC1R haplotypes can help discriminate between white and fawn coats in JD. We hope this report will trigger research on the genetics of this traditional Korean dog and will be a reference for dogs of Asian origin. Also, this study provides a useful genetic marker for JD breeders who have selected for specific coat colors.

ACKNOWLEDGMENT

This work was supported by the "Genome research on the Korean Jindo dog to be utilized as a working dog" project of the National Institute of Animal Science, RDA, Korea.

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