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Evidence of genetic contribution to patellar luxation in Toy Poodle puppies

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ABSTRACT. Patellar luxation (PL) is one of the most common orthopedic disorders in dogs and a genetic factor is considered to play an important role in the development of PL. Genomic analysis has attempted to identify the genetic markers associated with the development of PL but only suggestive markers have been identified. Carefully selecting breeds with higher incidence rates of congenital PL as well as affected dogs with more severe symptoms are required, but such information remains limited to date. This study aimed to assess the genetic contribution to the development of PL in puppies. Using data on PL from 2,048 puppies of the nine common breeds in Japan, the association of PL grades between the limbs, breed, and sex as well as the concordance of PL between littermates were examined. A significant correlation was found between right and left limbs in PL grades in all the puppies (Spearman rank correlation coefficient (r_s)=0.91, P<0.001) and for each breed (r_s=0.81–0.93, P<0.001). In total, 20.3% of the puppies were affected. The inter-breed difference in PL prevalence was 2.1–38.1%, and Toy Poodles showed the highest prevalence rates. Littermates of the affected puppies with PL grade ≥2 had a 16.2-fold higher risk (P<0.001). Thus, these results suggest that PL in puppies is primarily influenced by genetics, especially in Toy Poodles. These data highlight the necessity of using a breeding scheme to decrease the prevalence of PL.

KEY WORDS: genetic contribution, patellar luxation, puppy, Toy Poodle

Patellar luxation (PL) is one of the most common orthopedic disorders in small breed dogs [18]. PL leads to lameness, osteoarthritis, pain, and stress on the cranial cruciate ligament [3, 11, 15]. Although congenital and traumatic factors are involved, most PLs are considered congenital because they occur early in life and are not associated with trauma [4]. Although there are surgical techniques to correct PL, growing concern exists regarding the complications and re-luxation associated with surgery, especially in higher-grade PL [1, 2,6–9, 16, 22]. A breeding scheme is an alternative solution that has been used to decrease the prevalence of PL [11]. One approach that has worked well with PL is using healthier dogs for breeding. Between 1992 and 1998, the incidence rate of PL in Dutch Flat-Coated Retrievers dramatically decreased from 28 to 18% due to improved screening and breeding [11]; however, these rates did not improve from 1998 to 2006.

The identification of genetic markers associated with the development of PL could be extremely valuable for the development of a successful breeding scheme. Therefore, genetic analyses, including linkage analysis and genome-wide association studies (GWAS) have been performed in Flat-Coated Retrievers [12], Pomeranians [21, 24], and Kooikerhondje dogs [25]. It is worth noting that detailed information about PL grades was not considered in these investigations. However, these studies identified only suggestive markers. An increase in the statistical power to identify significant genetic markers could be achieved by increasing the sample sizes and carefully selecting breeds with a higher incidence of congenital PL and affected dogs with higher PL grade, and such information is required.

The purpose of this study was to assess the contribution of genetic factors in the development of PL from a large number of puppies of common breeds in Japan to overcome such limited information. We hypothesized that large-scale data would provide useful information for decreasing the prevalence of PL. We evaluated the association between right and left limbs in PL grades, and differences in the prevalence of PL according to sex and breed. We specifically focused on the concordance of disease status between littermates as sibling disease risk has been commonly used as an indicator of genetic contribution in humans [14] and dogs [23]. Sibling risk in humans has been used to motivate further genetic analysis such as linkage analysis and GWAS. To increase the sample size and diminish other confounding effects, we used information from medical checkups of puppies in dog auctions as we could access all siblings at the same time as assessed by the same veterinarian.

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MATERIALS AND METHODS

As this study included only a retrospective analysis of medical checkup data about auscultation, cornea, conjunctiva, and PL routinely obtained in pet's auctions, it was not considered animal research; therefore, we considered that ethics committee approval was not required for this study.

Study population and grading of PL

We examined 2,048 puppies comprising nine dog breeds (Toy Poodle, Chihuahua, Miniature Dachshund, Shiba, Pomeranian, Yorkshire Terrier, Maltese, Golden Retriever, and Labrador Retriever) in Japan from May 22, 2013 to January 22, 2014. Questionnaires were administered to dog breeders to obtain information on the animal species, breed, breeder's name, the day of medical checkup, date of birth, age, sex, birth place, and coat color. Veterinarians also completed the results of medical checkup about grades of PL, auscultation, cornea, and conjunctiva. Puppies were considered littermates if they had the same breeder, breed, date of birth, day of medical checkup, and consistent coat color.

PL grades were established by examining each puppy in a standing position and palpating the stifle joint. Veterinarians belonging to Anicom Insurance Inc. conducted all the examinations and classified each limb separately into five grades (0–4) based on the classification system developed by Putnam [19] (Supplementary Table 1). When PL grades were different between the limbs, the worse grade was used as the representative PL grade for further analysis, following [23]. Dogs with PL grade ≥1 were considered to be affected.

Statistical analysis

For the evaluation of the association of PL grades between right and left limbs, and differences in the prevalence of PL according to sex and breed, we randomly selected one puppy from each litter using the RAND function in Excel (Microsoft Corp., Tokyo, Japan) as the number of puppies per litter ranged from 1 to 9, and the potential bias of the number of puppies per litter may influence the statistical analyses in this study if PL in puppies was influenced by genetic factors. In total, we examined 1,174 puppies for further analysis. Spearman rank correlation coefficient was used to analyze the association of PL grades between both limbs. Sex differences in the prevalence of PL were examined using the Fisher's exact test with the same 1,174 puppies. We used Fisher's exact test to examine PL concordance between two randomly selected littermates from each litter. If a litter included three or more puppies, two were randomly selected for analysis. We analyzed the concordance of PL between two littermates of Toy Poodles, Shibas, and Yorkshire Terriers. The analysis of the concordance of PL grade ≥2 was also performed by removing the puppies affected with grade 1 PL as grade 1 is not unaffected in a strict sense [1]. SPSS version 23 (IBM Corp., Tokyo, Japan) was used to perform all statistical analyses. *P*-values <0.05 were considered significant in all statistical analyses.

RESULTS

We analyzed 2,048 puppies from 1,174 litters. The number of puppies per litter ranged from 1 to 9. Information on each breed is shown in Supplementary Table 2. The mean and median ages of the puppies were 43 and 42 days, respectively (range, 20–77). Of the puppies, 54.3% (1,113) were male and 45.7% (935) were female. Breeds included Toy Poodles (n=577), Chihuahuas (n=359), Miniature Dachshunds (n=286), Shibas (n=228), Pomeranians (n=163), Yorkshire Terriers (n=137), Maltese (n=109), Golden Retrievers (n=103), and Labrador Retrievers (n=86). We randomly selected one puppy from each litter to examine the association of PL grades between right and left limbs. PL grades between right and left limbs are shown in Fig. 1A. We found a significant correlation between right and left limbs in PL grades (Spearman rank correlation coefficient (r_s)=0.91, P<0.001). Among the 1,174 puppies studied, 205 (17.5%) had both the limbs affected, 33 (2.8%) had unilateral PL and 936 (79.7%) were not affected. The proportion of bilateral PL (86.1%) was significantly higher than that of unilateral PL (13.9%, P<0.001).

When analyzing each breed separately, we observed a significant correlation between right and left limbs in PL grades in Toy Poodles (r_s=0.93, P<0.001), Shibas (r_s=0.88, P<0.001), Pomeranians (r_s=0.89, P<0.001), Yorkshire Terriers (r_s=0.83, P<0.001), and Chihuahuas (r_s=0.81, P<0.001) (Fig. 1B–F). Because the number of affected puppies was small, we could not examine the correlation between right and left limbs in PL grades in the remaining four breeds (Miniature Dachshunds, Maltese, and Golden and Labrador Retrievers).

We determined the prevalence of affected puppies in the same 1,174 puppies that were randomly selected from each litter for the abovementioned correlation analysis. In total, 20.3% of puppies were affected with PL. The proportions of puppies with PL grades 1, 2, 3, and 4 were 12.9, 4.9, 2.1, and 0.3%, respectively. Table 1 shows the breed differences in the prevalence of affected puppies. Toy Poodles had the highest prevalence (38.1%), followed by Shibas (34.9%), Pomeranians (26.9%), Yorkshire Terriers (18.3%), Chihuahuas (8.6%), Golden Retrievers (5.7%), Miniature Dachshunds (3.5%), Labrador Retrievers (2.4%), and Maltese (2.1%). In addition, no sex differences were observed in PL prevalence in any of the breeds on multiple testing; however, the *P*-value of Pomeranians showed less than 0.05 although it did not pass the threshold after Bonferroni correction (*P*=0.016; Supplementary Table 3).

Next, we analyzed the concordance of PL between two littermates to determine a genetic influence. If a litter included three or more puppies, two were randomly selected for analysis. In total, 144 litter pairs of Toy Poodles were analyzed, of which 51 affected and 93 unaffected puppies were observed when one puppy of each litter pair was selected. Among the 51 affected puppies, 33 littermates (64.7%) were affected, while only 21 littermates (22.6%) of the 93 unaffected puppies were affected (Table 2).

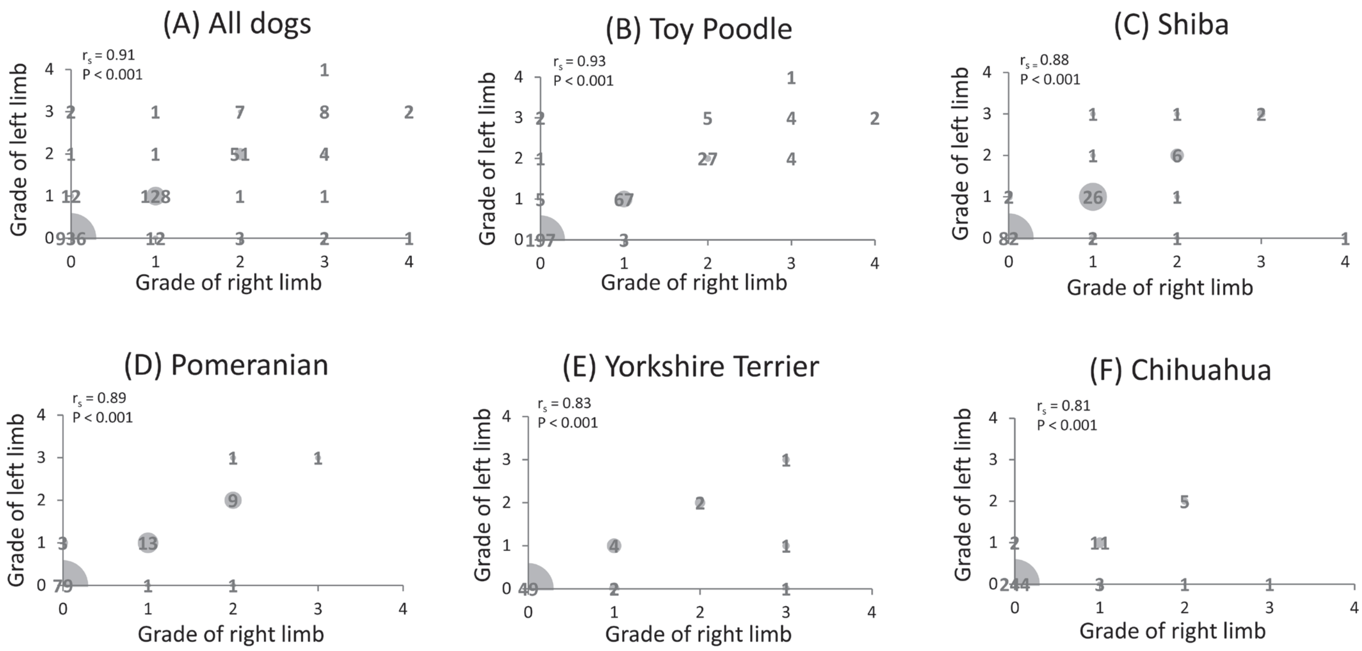

Fig. 1. The correlation of the grade of congenital patellar luxation between the limbs. The red number in each figure shows the numbers of puppies, and the size of the blue circle corresponds to the red numbers. All dogs in "A" represent the nine breeds included in this study; Toy Poodle, Chihuahua, Miniature Dachshund, Shiba, Pomeranian, Yorkshire Terrier, Maltese, Golden Retriever and Labrador Retriever.

Table 1. Distribution of patellar luxation (PL) grades in nine breeds of puppy examined in Japan

Breeds	Number of dogs	PL Grades					Affected dogs (grade ≥1)
		0	1	2	3	4	
Toy Poodle	318	61.9%	23.6%	8.8%	4.7%	0.9%	38.1%
Shiba	126	65.1%	23.8%	7.1%	3.2%	0.8%	34.9%
Pomeranian	108	73.1%	15.7%	9.3%	1.9%	0.0%	26.9%
Yorkshire Terrier	60	81.7%	10.0%	3.3%	5.0%	0.0%	18.3%
Chihuahua	267	91.4%	6.0%	2.2%	0.4%	0.0%	8.6%
Golden Retriever	35	94.3%	0.0%	5.7%	0.0%	0.0%	5.7%
Miniature Dachshund	171	96.5%	3.5%	0.0%	0.0%	0.0%	3.5%
Labrador Retriever	42	97.6%	2.4%	0.0%	0.0%	0.0%	2.4%
Maltese	47	97.9%	2.1%	0.0%	0.0%	0.0%	2.1%
Total	1,174	79.7%	12.9%	4.9%	2.1%	0.3%	20.3%

The littermates of affected Toy Poodle puppies had a 6.3-fold higher risk of PL (P<0.001, confidential interval (CI): 3.0–13.3). Conversely, we observed no significant difference in PL concordance between two littermates in Shibas (P=0.068, odds ratio (OR)=3.3, CI: 1.0–10.4) or Yorkshire Terriers (P=0.174, OR=3.8, CI: 0.7–20.0) (Table 2). The number of litter pairs of the other breeds was not sufficient for analysis.

We changed the threshold of PL grade from 1 to 2 and analyzed the concordance of PL (grade ≥2) between two littermates of Toy Poodles, Shibas, and Yorkshire Terriers. Since grade 1 is not unaffected in a strict sense, we removed dogs with grade 1 from this analysis. Among the 106 litter pairs of Toy Poodles, 14 affected and 92 unaffected puppies were observed when one puppy of each litter pair was selected. Eight littermates (57.1%) were affected among the 14 affected puppies, while only seven littermates (7.6%) of 92 unaffected puppies were affected (Table 3). Therefore, littermates of the affected puppies had a 16.2-fold higher risk of PL (P<0.001, CI: 4.4–60.0), and this tendency was observed in Shibas (P=0.07, OR=10.0, CI: 1.1–91.4), and Yorkshire Terriers (P=0.053, OR=18.0, CI: 1.2–262.7), although the number of affected puppies was low (Table 3).

DISCUSSION

We examined PL data for 2,048 puppies representing the nine common breeds in Japan and observed a strong correlation of PL grade between both limbs. There were large differences in the prevalence of PL among all breeds. Toy Poodles, Shibas, Pomeranians, and Yorkshire Terriers had a higher prevalence while the other breeds showed less than 10% prevalence.

Table 2. Concordance of patellar luxation of grade ≥1 among littermates of Toy Poodles, Shibas, and Yorkshire Terriers

(A) Toy Poodle

		Litter 2		
		Affected	Unaffected	Proportion of affected dogs (%)
Litter 1	Affected	33	18	64.7
	Unaffected	21	72	22.6

P<0.001, OR=6.3 (95% CI: 3.0–13.3).

(B) Shiba

		Litter 2		
		Affected	Unaffected	Proportion of affected dogs (%)
Litter 1	Affected	9	12	42.9
	Unaffected	8	35	18.6

P=0.068, OR=3.3 (95% CI: 1.0–10.4).

(C) Yorkshire Terrier

		Litter 2		
		Affected	Unaffected	Proportion of affected dogs (%)
Litter 1	Affected	4	4	50.0
	Unaffected	6	23	20.7

P=0.174, OR=3.8 (95% CI: 0.7–20.0).

OR, odds ratio; 95% CI, 95% confidential interval.

Table 3. Concordance of patellar luxation of grade ≥2 among littermates of Toy Poodles, Shibas, and Yorkshire Terriers

(A) Toy Poodle

		Litter 2		
		Affected	Unaffected	Proportion of affected dogs (%)
Litter 1	Affected	8	6	57.1
	Unaffected	7	85	7.6

P<0.001, OR=16.2 (95% CI: 4.4–60.0).

(B) Shiba

		Litter 2		
		Affected	Unaffected	Proportion of affected dogs (%)
Litter 1	Affected	2	2	50.0
	Unaffected	4	40	9.1

P=0.07, OR=10.0 (95% CI: 1.1–91.4).

(C) Yorkshire Terrier

		Litter 2		
		Affected	Unaffected	Proportion of affected dogs (%)
Litter 1	Affected	2	3	40.0
	Unaffected	1	27	3.6

P=0.053, OR=18.0 (95% CI: 1.2–262.7).

OR, odds ratio; 95% CI, 95% confidential interval.

Concordance analysis between littermates of the breeds showed that littermates of puppies with a PL grade ≥2 had a 16.2-fold higher risk of PL in Toy Poodles.

Previous investigations have revealed a high incidence of PL in small dog breeds, including Poodles, Yorkshire Terriers, Pomeranians, Chihuahua, and Maltese [5, 10, 15, 18]. Our results showed large differences (38.1% of the prevalence in Toy Poodles vs. 2.1% in Maltese) even in smaller breeds. These differences may be attributed, at least in part, to variations between puppies and adult dogs, and therefore, further inquiry is required to fully elucidate how PL changes across the lifespan of the dog.

Sex differences in PL incidence show considerable variability in the literature, with females more affected than male dogs in some [1, 11, 15, 18, 21], while males are more affected than female dogs in others [9]. Furthermore, some investigations report no sex differences [24, 25]. Our results revealed a significant sex difference only in Pomeranians. However, this result did not

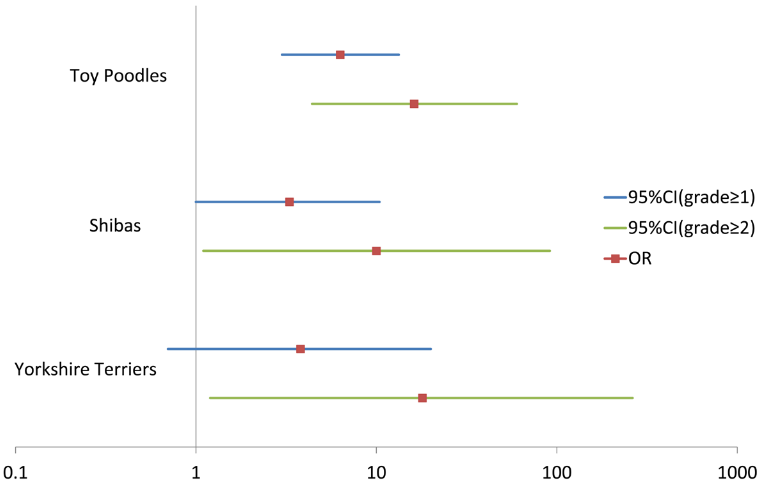

Fig. 2. The comparison of sibling risk of affected dogs with grades ≥1 and ≥2 patellar luxation. The blue and green lines in Fig. 2 show a 95% CI of concordance risk between littermates with grade ≥1 and grade ≥2 PL. The red blots show OR of concordance risk between littermates with grade ≥1 and grade ≥2 PL. The 95% CIs in the abscissa axis were represented by logarithmic numbers. OR, odds ratio; 95% CI, confidential interval.

remain significant after Bonferroni correction (*P*=0.016; Supplementary Table 3). This disparity may also be caused by a difference between puppies and adult dogs. This facet should be the focus of future investigations using basic epidemiological data.

We compared the prevalence rates of bilateral and unilateral PLs with those published previously and observed a strong correlation between right and left limbs in PL grades (r_s=0.91), with bilateral PL being more common than unilateral PL. The prevalence rates of bilateral and unilateral PLs varied among studies, i.e., they were equal in some studies [1, 9], unilateral PL was more common in some [20] and bilateral PL was more common in others [21, 25]. The large difference in the proportion of bilateral PL could be explained by the selection of dogs. Studies showing equal prevalence rates included dogs of various breeds and ages. Studies showing unilateral and bilateral PLs were more common when investigating large breed dogs or Pomeranians, respectively. We used nine breeds but focused only on puppies aged 20–77 days. The high prevalence of bilateral PL observed in this study suggests a genetic contribution to PL development in these puppies, as shown previously [11, 12, 24].

Analysis revealed a 6.3-fold higher risk in Toy Poodle littermates of affected puppies. This result also supported the idea that PL in puppies is genetically influenced because sibling disease risk has been commonly used as an indicator of genetic contribution in humans and dogs [14, 23]. This increased risk was as high as that in the highest risk breed (Pomeranians, 6.5) when compared with crossbreeds documented in a previous study [15]. Interestingly, the risk for littermates of affected puppies with PL grade ≥2 increased to 16.2. As shown in Fig. 2, this tendency was observed in other breeds, suggesting that PL grade ≥2 would be more influenced by genetics, whereas grade 1 may be also be caused by other factors such as traumatic factors [5] and patellar instability caused by an immature skeleton [17]. This result suggests that only dogs with PL grade ≥2 should be used to increase statistical power in genetic analysis.

In this study, we observed a high proportion of dogs with bilateral PL and higher risk for siblings, which suggest that PL in puppies is a heritable trait. These results suggest that genetic factors contributed to PL development in puppies, especially Toy Poodles. Therefore, a breeding scheme should be initiated to decrease the prevalence of PL. One method is to use only healthy dogs for breeding, and this method previously worked well to some extent in decreasing the incidence of PL in Dutch Flat-Coated Retrievers [11]; however, the incidence rates did not improve indefinitely. A more reliable method would be the use of genetic markers, especially causative pathogenic variants. Genetic markers have been shown to successfully reduce disease prevalence in neuronal ceroid lipofuscinosis in Border Collies in Japan [13]. Because the causative pathogenic variants for PL have not been identified in previous linkage analysis and GWAS [12, 21, 24, 25], this should be the focus of future studies. Based on the current data, Toy Poodle puppies will be useful samples for future genomic analysis of PL in Japan because their PL prevalence was the highest and disease concordance between littermates was high. In particular, use of patient dogs with PL grade ≥2 as cases would provide higher statistical power as there would be a higher disease risk in littermates. Selection of controls should be carefully performed because of high disease prevalence. This kind of large-scale data would also be useful for designing a breeding scheme.

Limitations of this study are related to its retrospective design. Recorded data were dependent on the accuracy of the medical checkup data. All palpations for PL grading are performed only in a standing position, not palpation of both standing position and lateral recumbence, or using imaging techniques (radiography, and CT). Palpation for PL in lateral recumbence is suitable to examine medial or lateral PL because muscle tension can prevent luxating patella [5]. Also, imaging techniques (radiography and CT) are suitable to identify any skeletal abnormalities [5]. These types of imaging may reveal the detailed mechanism of PL, which might lead to accurate concordance analysis using groups affected by the same mechanism. However, there would not be a major error in PL grading because it was performed according to the classification system developed by Putnam. Our results suggest that genetic factors contribute to PL development in Toy Poodle puppies. However, this result may not apply to Toy Poodles in other countries because the prevalence of genetic diseases is often different between regions due to genetic stratification. For example, the PL incidence rates in Labrador Retrievers vary considerably across countries. The incidence rates were low in United States of America [10] and England [15], but high in South Korea [1]. Since some breeds might show higher PL incidence rates and a strong risk for the siblings in other countries, it would be better to examine the PL incident rates and sibling risk before genetic analyses are performed. Furthermore, statistical analyses were limited in the number of some breeds. If their numbers were increased, other breeds might also be found at risk as high as Toy Poodles in this study.

In conclusion, these results suggest a genetic contribution to PL. Therefore, PL in puppies is influenced by genetic factors, especially in Toy Poodles. A breeding scheme including the use of healthy dogs for breeding and the introduction of genetic testing is necessary to decrease the prevalence of PL.

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