Population genetic analysis and genome-wide association study of patellar luxation in a Thai population of Pomeranian dogs

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ABSTRACT

The genetics of patellar luxation (PL) were investigated in Pomeranian dogs presented at the Small Animal Hospital, Faculty of Veterinary Science, Chulalongkorn University. A cohort of 339 Pomeranian dogs, part of a four-generation pedigree of 842 Pomeranians, was screened for PL from 2006 to 2013. PL was present in 77% of the screened dogs, with 84% having bilateral and 16% unilateral luxation. Medial PL was more common (95%) than lateral PL (2%) or bidirectional PL (3%). The risk of PL was similar in male and female dogs (female:male relative risk 1.11, 95% CI 0.98–1.25). The heritability of PL in the screened population was 0.44 ± 0.04 using a threshold model. A genome-wide association study of PL (48 cases and 48 controls) using a high-density SNP array indicated the possible involvement of 15 chromosomal regions, of which CFA05 and CFA32 remained associated in a larger study involving an additional 128 cases and 7 controls. Candidate genes in these regions may be involved in the pathogenesis of PL in Pomeranian dogs.

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1. Introduction

Congenital patellar luxation (PL) in dogs, a developmental disorder, is thought to be a multifactorial inherited disease (LaFond et al., 2002). It is most common in small-breed dogs, and in Thailand the prevalence of medial patellar luxation (MPL) and lateral patellar luxation (LPL) in small-breed dogs is 87% and 13%, respectively (Wangdee et al., 2005; Wangdee and Kalpravidh, 2008). Pomeranian dogs are currently the highest-ranking breed for PL in the USA, with 37.2% of dogs reported to be affected (OFA, 2015). In Thailand, 75% of the Pomeranian dog population is affected (Soontornvipart et al., 2013). This breed predisposition suggests that the disease is inherited in Pomeranians (Priester, 1972; LaFond et al., 2002; Alam et al., 2007; OFA, 2015; Soontornvipart et al., 2013). In small-breed dogs, PL is more common in female dogs than in male dogs, with a female:male ratio of up to 1.9 (DeAngelis and Hohn, 1970; Priester, 1972; Hulse, 1993; Hayes et al., 1994; Alam et al., 2007; Linney et al., 2011; Soontornvipart et al., 2013). In contrast, in large-breed dogs, the female:male ratio of dogs with PL can be as low as 0.56 (Remedios et al., 1992; Gibbons et al., 2006; Arthurs and Langley-Hobbs, 2007). One exception was reported by Lavrijsen et al.

(2013), who showed that female Flat-Coated Retrievers were at higher risk of PL than male dogs (relative risk = 1.8). These sex differences suggest that PL might be influenced by hormone factors and/or X-linked factors (Priester, 1972). A preliminary genome-wide association study with Pomeranians suggested that a region on CFA07 is involved in MPL (Soontornvipart et al., 2013); however, the limited number of SNPs used meant that only loci with a large effect on the phenotype could be detected.

The aims of this study were to investigate the prevalence of PL in a cohort of Thai Pomeranians and to estimate its heritability. In addition, a genome-wide association analysis was performed to identify multiple chromosomal regions involved in the development and aetiology of MPL. Subsequently, selected SNPs were tested in a large population of Thai Pomeranians and in dogs of other breeds.

2. Materials and methods

2.1. Animals

Pomeranians referred to the Small Animal Hospital, Faculty of Veterinary Science, Chulalongkorn University, Thailand, were screened for PL from 2006 to 2013. The pedigrees of 842 Pomeranian dogs from four generations were recorded. Blood samples (4 ml) were collected from 339 of these Pomeranians for DNA analysis in the genetic study of PL;

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all dogs were investigated using a standard orthopaedic protocol ([Piermattei et al., 2006](#)). The dogs were included with informed consent of the owners. In dogs with medial and/or lateral PL in the right and/or left hind leg, respectively, PL was graded with the dogs standing and in lateral recumbency, using a PL grading system (grades I to IV) ([Piermattei et al., 2006](#)). In grade I PL, the patella can be manually luxated in full extension of the stifle joint, returning to the normal position when released. In grade II PL, the patella luxates more frequently than in grade I. The patella luxates easily, especially when the foot and tibia are rotated, while the patella is pushed in a medial or pulled in a lateral direction. Reduction occurs with the opposite manoeuvres. In grade III PL, the patella is permanently luxated, but can manually be reduced with the stifle in extension; however, flexion and extension of the stifle result in reluxation of the patella. In grade IV PL, the patella is permanently luxated and cannot be manually repositioned. Bidirectional patellar luxation (BPL) is defined when the patella of the same stifle luxates both medially and laterally.

The female-to-male ratio in the affected group was calculated. Since more female than male dogs were tested, the relative risk (RR) was calculated according to $RR = (a_1 / n_1) / (a_0 / n_0)$ where a_1 is the number of exposed female dogs with the disease, a_0 is the number of exposed male dogs with the disease, n_1 is the total number of exposed female dogs, and n_0 is the total number of exposed male dogs. A RR of 1 indicates that the risk is the same in female and male dogs, a RR < 1 means that female dogs are at lower risk than male dogs, and a RR > 1 means that female dogs are at higher risk than male dogs ([Priester, 1972; Dohoo et al., 2010](#)).

2.2. Heritability of patellar luxation

Phenotypic score of PL was set to 0 for unaffected and 1 for affected. Variance components (σ^2) and the resulting heritability of PL in the Pomeranian dogs were calculated with the program ASReml ([Gilmour et al., 1995](#)) using the following repeated measurement threshold model:

$$\text{Logit}\left(p_{ij}\right) = \mu + \text{animal}_i + pe_i$$

where p_{ij} is the probability that the stifle for dog i ($i = 1, …, 339$) on side j ($j = 1, 2$) has PL (PL = 1) or not (PL = 0), μ is the overall mean. Fixed effects were tested with an F-statistic, with $P < 0.05$ being considered significant. Preliminary analysis showed that animal sex and coat colour were not significant variables and they were excluded from the model. Random effects included polygenic animal (animal_i) and permanent environment (pe_i). Since each dog has two stifles and both scores were included in the analysis an additional factor (pe) was included in the model to account for non-genetic effects that might affect both stifles on the same dog such as feeding, rearing etc. Normal distributions were assumed for the random effect models: animal ~ N(0, Aσ^2_a), pe ~N (0, Iσ^2_{pe}), where A contains the additive genetic relationship between animals and I is an identity matrix of appropriate size. The relationship matrix was constructed using 842 Pomeranians pedigree records. In the threshold model, the residual variance (σ^2_e) was fixed at 3.289. Heritability on the underlying scale was calculated using the formula ([Falconer, 1981](#)):

$$h^2 = \text{additive genetic variation/phenotypic variation}$$
$$= \sigma_a^2/(\sigma_a^2 + \sigma_{pe}^2 + \sigma_e^2)$$

2.3. Association study

The DNA samples of unrelated 96 Pomeranian selected from the cohort of 339 dogs were genotyped with Illumina CanineHD BeadChip, which contains 173,662 SNPs. Of these 96 dogs, 48 had MPL and 48

were unaffected controls. Genotype data were analysed for Hardy-Weinberg equilibrium with an inclusion threshold of $P \geq 0.01$. SNPs with a minor allele frequency below 5% and a genotyping success rate below 95% were excluded, as well as individual dogs with >10% missing genotypes. Plink v1.07 software ([Purcell et al., 2007](#)) was used for allelic association testing. Population stratification was assessed by calculating the genomic inflation factor. None of the case and control dogs shared parents, thereby avoiding family stratification. Allele frequencies of SNPs were compared between cases and controls using a standard Chi-square based test. Results were corrected empirically by max(T) permutation with 1000 swaps of the phenotype (EMP1) and for multiple testing by comparing the permutation result of an individual SNP against that of all other SNPs (EMP2).

A competitive allele-specific PCR was used to genotype SNPs from regions of interest in a validation group of an additional 128 affected and 7 control Pomeranian dogs selected from unrelated cohort of 339 dogs. KASP™ chemistry (LGC genomics, Hoddesdon, UK) was used to generate allele-specific fluorescent signals as instructed by the manufacturer. The signals were recorded and scored using a BIORAD MYiQ2 iCycler (BIO-RAD, Herts, UK). A χ^2 test was used to compare the allele frequencies of these SNPs in cases and controls from the validation cohort and from the first group of 96 dogs included in the genome-wide association study. These SNPs were also genotyped additionally in 3 breeds from the Netherlands and in 2 breeds from Thailand including 32 PL case and 32 control Dutch Kooiker dogs, 32 case and 32 control Dutch Flat-Coated Retrievers, 16 case and 23 control Dutch Labrador Retrievers, 24 case and 8 control Thai Chihuahuas, and 23 case and 9 control Thai Miniature Poodles.

3. Results

3.1. Animals and phenotyping

Of the 202 female and 137 male Pomeranians investigated, 261 (77%) had PL (Table 1): 220 (84.3%) bilaterally and 41 (15.7%) unilaterally. Overall, 80% of the female dogs and 72% of the male dogs were affected, giving a RR of 1.11 (95% CI 0.98–1.25), which means that female dogs were not at significantly higher risk of PL than male dogs. Of 481 affected stifle joints, 94.8% displayed MPL, 2.3% LPL, and 2.9% BPL. The severity of PL varied from grade I to grade IV (Table 2).

3.2. Heritability

The heritability on the underlying scale of PL was 0.44 ± 0.04 in this Pomeranian dog population.

3.3. Genome-wide association analysis

Of the 173,662 SNPs represented on the canine HD array, we excluded 45,366 non-informative SNPs, 6131 SNPs with a genotyping rate below 95%, and 1313 SNPs based on deviation from Hardy-Weinberg equilibrium. The remaining 123,456 SNPs were used to construct an identical-by-state (IBS) plot, based on the first two principal components of the multidimensional IBS matrix (Supplementary Fig. 1). The Pomeranian sample set was highly stratified with a genomic inflation

Table 1
Prevalence of patellar luxation (PL) in Pomeranian dogs in Thailand from 2006 to 2013.

Status	Number (%)		
	Female	Male	Subtotal
Normal	40 (19.8%)	38 (27.7%)	78 (23%)
Patellar luxation	162 (80.2%)	99 (72.3%)	261 (77%)
- Bilateral PL	134	86	220 (84.3%)
- Unilateral PL	28	13	41 (15.7%)
Total	202 (100%)	137 (100%)	339 (100%)

Table 2
Direction and severity of patellar luxation (PL) in Pomeranian dogs in Thailand from 2006 to 2013.

	Number (%) of stifle joints affected with PL
Direction of luxation	
Medial PL	456 (94.8%)
Lateral PL	11 (2.3%)
Bidirectional PL	14 (2.9%)
Total	481 (100%)
Grade of PL[a]	
Grade I	136 (28.3%)
Grade II	210 (43.6%)
Grade III	98 (20.4%)
Grade IV	37 (7.7%)

[a] Grading system according to Piermattei et al. (2006).

factor of 1.46. Sixteen samples that deviated from the main population were excluded, leaving data for 44 cases and 36 controls for further analysis and reducing the genomic inflation factor to 1.09.

One single SNP on chromosome 13 displayed allelic association with MPL, using PLINK and the case/control phenotype, with $P = 4.32 \times 10^{-5}$ (Fig. 1). After correction using permutations of the phenotype, $P = 9.9 \times 10^{-4}$ and after max(T) correction for multiple testing $P = 0.3107$ (Table 3). The association of this SNP was then investigated in the validation cohort of 128 new cases and 7 new controls. In addition, another 21 SNPs on chromosomes CFA02, CFA03, CFA05, CFA06, CFA07, CFA08, CFA09, CFA11, CFA17, CFA21, CFA24, CFA28, CFA32, and CFA37 with $P \leq 3.0 \times 10^{-3}$ were analysed in the validation cohort. In Pomeranians, the association signal of the SNP located at position CFA05:12113130 with PL improved from a Chi-square P of 1.09×10^{-4} to 1.39×10^{-5}. The association of another SNP (BICF2G630594583) located at position CFA32:17832518 with PL slightly decreased with a Chi-square P from 7.37×10^{-6} to 3.72×10^{-5} (Table 3). These SNPs were not associated with PL in the cohorts of Kooiker dogs, Flat-Coated Retrievers, Labrador Retrievers, Chihuahuas, and Miniature Poodles.

4. Discussion

PL is one of the most common orthopaedic problems found in Pomeranians, both in the USA (OFA, 2015) and in Thailand (Soontornvipart et al., 2013), where it has a prevalence of 39.5% and 77%, respectively. In this study of Pomeranians from Thailand, bilateral luxation (84%) was found to be five times more common than unilateral luxation (16%). This level of bilateral luxation is higher than that reported in other populations of small dogs, which had equal (50/50) levels of unilateral and bilateral PL (Remedios et al., 1992; Arthurs and Langley-Hobbs, 2006; Gibbons et al., 2006; Alam et al., 2007; Arthurs and Langley-Hobbs,

2007; Linney et al., 2011). PL was equally common in male and female Pomeranians, with a RR of 1.11 (95% CI 0.98–1.25), which is lower than that reported by Priester (1972), who investigated a heterogeneous cohort of 400 small-breed, 31 medium-breed, and 48 large-breed dogs of 33 different breeds including 37 Pomeranians (11 males and 26 females). MPL was more common than LPL, which is consistent with other reports in both small- and large-breed dogs (Remedios et al., 1992; Roush, 1993; Hayes et al., 1994; Gibbons et al., 2006; Alam et al., 2007). The only exception is a report by Lavijsen et al. (2013), who found LPL to be more common than MPL in Flat-Coated Retrievers. BPL was diagnosed in 2.9% of Pomeranians, a lower proportion than that reported earlier for small- and miniature-breed dogs (6.5%) (Vidoni et al., 2006), Kooiker dogs (7%) (Wangdee et al., 2014), and Flat-Coated Retrievers (8%) (Lavrijsen et al., 2013).

The predisposition to PL of certain breeds and the substantial proportion of dogs with bilateral PL suggests that the disorder is heritable, and the lack of sex predisposition and a Mendelian segregation pattern point towards it being a polygenic disorder. The heritability estimate was 0.44 ± 0.04 in this Pomeranian dog population, indicating that genetic factors are important, given the h^2 values in other breeds, i.e. Kooiker Dogs with a h^2 of 0.27 ± 0.07 (Wangdee et al., 2014) and in Flat-Coated Retrievers with a h^2 of 0.17 ± 0.03 (Lavrijsen et al., 2013). It also indicates that environmental and residual variances play a role in the phenotypic appearance of the trait. This means that unaffected dogs can transmit susceptibility to the disorder to their offspring, which might limit the success rate of a breeding programme based solely on the exclusion of clinically affected animals.

The most strongly associated SNPs in the genome-wide association study were located on chromosomes CFA02, CFA03, CFA05, CFA06, CFA07, CFA08, CFA09, CFA11, CFA 13, CFA17, CFA21, CFA24, CFA28, CFA32, and CFA37. The association of the regions on CFA05 and CFA32 remained suggestive when a larger group of dogs was investigated (Table 3). It should be noted that the number of additional controls that were included was small (n = 7) in comparison to the number of added cases (n = 128). The power to detect association in the additional dogs as an independent group was therefore limited.

The genes of interest that may be involved in MPL in Pomeranians situated are SORL1 and SC5D in the associated region on CFA05 and BMPR1B and UNC5C in the region on CFA32. The SC5D gene on chromosome 5 encodes an enzyme of cholesterol biosynthesis. Mutations in this gene have been associated with lathosterolosis in humans, a disorder associated with multiple congenital anomalies including abnormal bone calcification, limb malformation, and liver disease (Kelley and Herman, 2001; Rossi et al., 2005; Rossi et al., 2007). The BMPR1B gene located on chromosome 32 encodes a member of the bone morphogenetic protein (BMP) receptor family of transmembrane serine/threonine kinases. BMPs are members of the TGF-beta superfamily, which are involved in endochondral bone formation and embryogenesis.
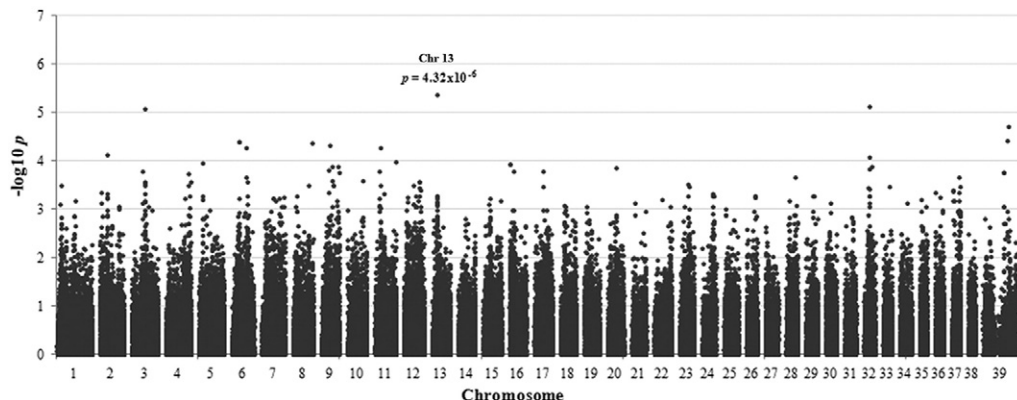

Fig. 1. Manhattan plot from genome-wide association analysis of patellar luxation in Pomeranians shows the highest association SNP on chromosome 13.

Table 3
Association analysis of 22 single nucleotide polymorphisms (SNPs) with patellar luxation in Pomeranians shows chi-square P of GWAS, validation, and combined groups.

SNPs	CFA	Location	GWAS[a]	EMP2	Validation[b]	Combined[c]
BICF2S22915306	02	26427387	7.584E-05	0.994	0.581626	0.000228
BICF2S23636260	02	27963936	0.001307	1	0.069802	0.001718
BICF2P6182	03	46818844	8.153E-06	0.5015	0.466603	0.011986
BICF2P634673	05	12113130	0.000109	0.998	0.685786	1.39E-05
BICF2P168471	06	26696828	4.023E-05	0.967	0.126111	0.000577
BICF2P679664	06	51594569	5.417E-05	0.988	0.55635	0.002011
BICF2P16241	07	38453221	0.0005938	1	0.125579	0.007447
BICF2S23448189	08	68907027	4.165E-05	0.974	0.448636	0.002452
BICF2P1057164	09	26538011	4.862E-05	0.982	0.474363	0.002994
BICF2G630837296	09	36636684	0.0001277	1	0.405024	0.004332
BICF2S23450786	09	60353163	0.0001689	1	0.592331	0.012755
BICF2G630296947	11	22079033	0.001246	1	0.428399	0.109985
BICF2G630610959	13	17345582	4.319E-06	0.3197	0.213454	0.000355
BICF2S23628004	17	32936920	0.0001657	1	0.589799	0.002452
BICF2P578758	21	41405505	0.002995	1	0.583165	0.214599
BICF2G630495865	24	46793211	0.0000457	0.976	0.647035	0.015248
BICF2S23616264	28	33475362	0.0002198	1	0.520898	0.0114
BICF2G630594583	32	17832518	7.371E-06	0.4326	0.095588	3.72E-05
BICF2P955649	32	17258231	8.185E-05	0.995	0.088086	0.060258
BICF2S23116545	32	25356964	0.0001284	1	0.351672	0.082033
BICF2G630130877	37	25338016	0.0002111	1	0.401866	0.000731
BICF2G630132832	37	27512126	0.0003403	1	0.177016	0.00018

[a] The cohort of 44 cases and 36 controls of GWAS.
[b] The cohort of 128 cases and 7 controls of validation group.
[c] The cohort of 172 cases and 43 controls of combined group.

Mutations in *BMPR1B* are associated with chrondrodysplasia (Demirhan et al., 2005). Further studies investigating the DNA sequence of this gene and *SC5D* in affected dogs are required to establish their involvement in the disease. An earlier study of PL in Pomeranians from Thailand suggested a SNP on chromosome 7 to be associated with MPL (Soontornvipart et al., 2013), but we could not confirm this association. The earlier study was probably underpowered because of the limited number of only 9 controls.

The loci identified in Pomeranians were not associated with PL in the cohorts of Dutch Kooiker dogs (Wangdee et al., 2014), Dutch Flat-Coated Retrievers (Lavrijsen et al., 2013), Dutch Labrador Retrievers, Thai Chihuahuas, and Thai Miniature Poodles. The loci involved in PL may be different in these breeds. Apparently many genes influence the PL status and the gene variants involved are not shared across breeds.

5. Conclusions

PL, and particularly MPL, is a widespread hereditary disease in Pomeranians. The heritability of PL in this population was 0.44, and regions on chromosome 5 and chromosome 32 were associated with the occurrence of MPL in these dogs, although genome-wide significance was not reached. The *SC5D* gene located on CFA05 and the *BMPR1B* gene located on CFA32 have been implicated in bone malformation and cartilage formation, and therefore are good candidate genes for a role in the pathogenesis of MPL in Pomeranians. Further research to confirm the role of either of the genes in PL is required.

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Conflict of interest statement

This is no conflict of interest.

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References

Alam, M.R., Lee, J.I., Kang, H.S., Kim, I.S., Park, S.Y., Lee, K.C., Kim, N.S., 2007. Frequency and distribution of patellar luxation in dogs. 134 cases (2000 to 2005). Vet. Comp. Orthop. Traumatol. 20, 59–64.

Arthurs, G.I., Langley-Hobbs, S.J., 2006. Complications associated with corrective surgery for patellar luxation in 109 dogs. Vet. Surg. 35, 559–566.

Arthurs, G.I., Langley-Hobbs, S.J., 2007. Patellar luxation as a complication of surgical intervention for the management of cranial cruciate ligament rupture in dogs. A retrospective study of 32 cases. Vet. Comp. Orthop. Traumatol. 20, 204–210.

DeAngelis, M., Hohn, R.B., 1970. Evaluation of surgical correction of canine patellar luxation in 142 cases. J. Am. Vet. Med. Assoc. 156, 587–594.

Demirhan, O., Turkmen, S., Schwabe, G.C., Soyupak, S., Akgul, E., Tastemir, D., Karahan, D., Mundlos, S., Lehmann, K., 2005. A homozygous BMPR1B mutation causes a new subtype of acromesomelic chondrodysplasia with genital anomalies. J. Med. Genet. 42, 314–317.

Dohoo, I., Martin, W., Stryhn, H., 2010. Measures of association. Veterinary Epidemiologic Research. Atlantic Veterinary College Inc., University of Prince Edward Island, Prince Edward Island, Canada, pp. 121–136.

Falconer, D.S., 1981. Heritability. Introduction to Quantitative Genetics, second ed. Longman Group Limited, Essex, UK, pp. 148–169.

Gibbons, S.E., Macias, C., Tonzing, M.A., Pinchbeck, G.L., McKee, W.M., 2006. Patellar luxation in 70 large breed dogs. J. Small Anim. Pract. 47, 3–9.

Gilmour, A.R., Thompson, R., Cullis, B.R., 1995. Average information REML: an efficient algorithm for variance parameter estimation in linear mixed models. Biometrics 51, 1440–1450.

Hayes, A.G., Boudrieau, R.J., Hungerford, L.L., 1994. Frequency and distribution of medial and lateral patellar luxation in dogs: 124 cases (1982–1992). J. Am. Vet. Med. Assoc. 205, 716–720.

Hulse, D.A., 1993. Medial patellar luxation in the dog. In: Bojrab, M.J. (Ed.), Disease Mechanisms in Small Animal Surgery, second ed. Lea&Febiger, Philadelphia, pp. 808–817.

Kelley, R.I., Herman, G.E., 2001. Inborn errors of sterol biosynthesis. Annu. Rev. Genomics Hum. Genet. 2, 299–341.

LaFond, E., Breur, G.J., Austin, C.C., 2002. Breed susceptibility for developmental orthopedic diseases in dogs. J. Am. Anim. Hosp. Assoc. 38, 467–477.

Lavrijsen, I.C., Heuven, H.C., Breur, G.J., Leegwater, P.A., Meutstege, F.J., Hazewinkel, H.A., 2013. Phenotypic and genetic trends of patellar luxation in Dutch Flat-Coated Retrievers. Anim. Genet. 44, 736–741.

Linney, W.R., Hammer, D.L., Shott, S., 2011. Surgical treatment of medial patellar luxation without femoral trochlear groove deepening procedures in dogs: 91 cases (1998–2009). J. Am. Vet. Med. Assoc. 238, 1168–1172.

OFA, 2015. Orthopedics Foundation for animal: Patellar luxation statistics. URL http://www.offa.org/stats_pl.html.

Piermattei, D.L., Flo, G.L., DeCamp, C.E., 2006. The stifle joint. In: Piermattei, D.L., Flo, G.L., DeCamp, C.E. (Eds.), Handbook of Small Animal Orthopedics and Fracture Repair, fourth ed. Saunders, St. Louis, pp. 562–632.

Priester, W.A., 1972. Sex, size, and breed as risk factors in canine patellar dislocation. J. Am. Vet. Med. Assoc. 160, 740–742.

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A.R., Bender, D., Maller, J., Sklar, P., de Bakker, P.I.W., Daly, M.J., Sham, P.C., 2007. PLINK: a toolset for whole-genome association and population-based linkage analysis. Am. J. Hum. Genet. 81, 559–575.

Remedios, A.M., Basher, A.W., Runyon, C.L., Fries, C.L., 1992. Medial patellar luxation in 16 large dogs. A retrospective study. Vet. Surg. 21, 5–9.

Rossi, M., Vajro, P., Iorio, R., Battagliese, A., Brunetti-Pierri, N., Corso, G., Di Rocco, M., Ferrari, P., Rivasi, F., Vecchione, R., Andria, G., Parenti, G., 2005. Characterization of liver involvement in defects of cholesterol biosynthesis: long-term follow-up and review. Am. J. Med. Genet. A 132A, 144–151.

Rossi, M., D'Armiento, M., Parisi, I., Ferrari, P., Hall, C.M., Cervasio, M., Rivasi, F., Balli, F., Vecchione, R., Corso, G., Andria, G., Parenti, G., 2007. Clinical phenotype of lathosterolosis. Am. J. Med. Genet. A 143A, 2371–2381.

Roush, J.K., 1993. Canine patellar luxation. Vet. Clin. North Am. 23, 855–868.

Soontornvipart, K., Wangdee, C., Kalpravidh, M., Brahmasa, A., Sarikaputi, M., Temwichitr, J., Lavrijsen, I.C., Theyse, L.F., Leegwater, P.A., Hazewinkel, H.A., 2013. Incidence and genetic aspects of patellar luxation in Pomeranian dogs in Thailand. Aust. Vet. J. 196 (1), 122–125.

Vidoni, B., Sommerfeld-Stur, I., Eisenmenger, E., 2006. Diagnostic and genetic aspects of patellar luxation in small and miniature breed dogs in Austria. Eur. J. Companion Anim. Pract. 16, 149–158.

Wangdee, C., Kalpravidh, M., 2008. Tube realignment for patellar luxation repair in dogs. Thai J. Vet. Med. 38, 39–44.

Wangdee, C., Soontornvipart, K., Chuthatep, S., 2005. Study of the canine patellar luxation surgical treatments. J. Thai Vet. Pract. 17, 13–25.

Wangdee, C., Leegwater, P.A., Heuven, H.C., van Steenbeek, F.G., Meutstege, F.J., Meij, B.P., Hazewinkel, H.A., 2014. Prevalence and genetics of patellar luxation in Kooiker dogs. Vet. J. 201 (3), 333–337.