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Breed distribution of the nt230(del4) *MDR1* mutation in dogs

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ABSTRACT

A 4-bp deletion mutation associated with multiple drug sensitivity exists in the canine multidrug resistance (*MDR1*) gene. This mutation has been detected in more than 10 purebred dog breeds as well as in mixed breed dogs. To evaluate the breed distribution of this mutation in Germany, 7378 dogs were screened, including 6999 purebred and 379 mixed breed dogs. The study included dog breeds that show close genetic relationship or share breeding history with one of the predisposed breeds but in which the occurrence of the *MDR1* mutation has not been reported. The breeds comprised Bearded Collies, Anatolian Shepherd Dog, Greyhound, Belgian Tervuren, Kelpie, Borzoi, Australian Cattle Dog and the Irish Wolfhound.

The *MDR1* mutation was not detected is any of these breeds, although it was found as expected in the Collie, Longhaired Whippet, Shetland Sheepdog, Miniature Australian Shepherd, Australian Shepherd, Wäller, White Swiss Shepherd, Old English Sheepdog and Border Collie with varying allelic frequencies for the mutant *MDR1* allele of 59%, 45%, 30%, 24%, 22%, 17%, 14%, 4% and 1%, respectively. Allelic frequencies of 8% and 2% were determined in herding breed mixes and unclassified mixed breeds, respectively.

Because of its widespread breed distribution and occurrence in many mixed breed dogs, it is difficult for veterinarians and dog owners to recognise whether *MDR1*-related drug sensitivity is relevant for an individual animal. This study provides a comprehensive overview of all affected dog breeds and many dog breeds that are probably unaffected on the basis of ~15,000 worldwide *MDR1* genotyping data.

Introduction

P-glycoprotein is an adenosine triphosphate (ATP)-driven drug efflux carrier, encoded by the multidrug resistance gene *MDR1*, also referred to as *ABCB1*. P-glycoprotein transports a broad variety of structurally diverse compounds that are usually hydrophilic and amphiphatic (Fromm, 2004), including many drugs commonly used in veterinary medicine (Mealey, 2004). The carrier is expressed in many tissues with secretory or excretory functions, such as the liver, kidney and intestine, where it limits drug absorption from the gut and promotes drug excretion into the bile and urine. Additionally, P-glycoprotein is highly expressed at the blood–brain barrier, where it restricts drug entry into the central nervous system (Thiebaut et al., 1987; Cordon-Cardo et al., 1990).

In 2001, a 4-bp gene deletion mutation was identified in the canine *MDR1* gene and was referred to as *mdr1-1Δ*, *ABCB1-1Δ*, or *MDR1* nt230(del4) (Mealey et al., 2001; Neff et al., 2004; Geyer et al., 2005a; Mealey and Meurs, 2008). This *MDR1* mutation correlates with the ivermectin-sensitive phenotype that was recognised in Collie dogs in the early 1980s (Seward, 1983; Pulliam et al., 1985). Dogs with homozygous nt230(del4) *MDR1* mutations do not express a functionally intact P-glycoprotein and (in addition to ivermectin) show increased sensitivity to many P-glycoprotein-transported drugs such as moxidectin, milbemycin oxime, acepromazine, butorphanol, digoxin, vincristine and loperamide (Martinez et al., 2008; Mealey, 2008).

Apart from the Collie, many additional dog breeds as well as mixed breed dogs are affected by this mutation (Neff et al., 2004; Geyer et al., 2005b; Mealey and Meurs, 2008) and it is therefore difficult for veterinarians and dog owners to recognise whether *MDR1*-related drug sensitivity is relevant for an individual animal. The purpose of the present study was to provide an overview of all affected as well as many of the most likely unaffected dog breeds on the basis of 7378 *MDR1* genotyping data from Germany and an additional 7500 cases reported in the literature from other countries.

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Materials and methods

Animals and blood samples

Blood samples were obtained from client-owned dogs and analysed for the nt230(del4) *MDR1* mutation as part of the diagnostic research service at our institute. In total, 7378 samples from 106 purebred dog breeds were analysed, including the following breeds (only breeds with at least 20 samples are listed): Collie ($n = 2227$), Australian Shepherd ($n = 1908$), Shetland Sheepdog ($n = 960$), Border Collie ($n = 527$), White Swiss Shepherd ($n = 274$), Anatolian Shepherd Dog ($n = 193$), Wäller ($n = 110$), Bearded Collie ($n = 79$), Greyhound ($n = 73$), Miniature Australian Shepherd ($n = 72$), Old English Sheepdog ($n = 67$), Australian Cattle Dog ($n = 52$), Irish Wolfhound ($n = 36$), Beagle ($n = 35$), Belgian Tervuren ($n = 33$), Borzoi ($n = 23$), Chinese Shar Pei ($n = 22$), Kelpie ($n = 20$) and Longhaired Whippet ($n = 20$).

Additionally, 261 herding breed mixes (dogs for which at least one parent was known to be a herding breed, such as a Collie or Border Collie) and 118 unclassified mixed breed dogs (for which the parentage was either unknown or no parental herding breed was present) were analysed. There were no samples from the English Shepherd, McNab or Silken Windhound breeds, which are uncommon in Germany but for which the nt230(del4) *MDR1* mutation has been identified (Neff et al., 2004; Mealey and Meurs, 2008). Dogs were included in the present study when the animal's name and breed were given by the owner or veterinarian. However, in general no effort was made to confirm the reported breed by inspecting the breeding documents.

MDR1 genotyping

Genomic DNA was isolated from 200 μL EDTA-preserved blood samples as reported previously (Geyer et al., 2005a). For *MDR1* genotyping, an automated fluorogenic 5′ nuclease TaqMan allelic discrimination method was used as described elsewhere (Klintzsch et al., 2009).

Results

A total of 7378 dogs from Germany were *MDR1* genotyped. More than half of all samples were derived from Collies and Australian Shepherds. Samples from Shetland Sheepdogs, Border Collies, White Swiss Shepherds, Wällers, Miniature Australian Shepherds and Old English Sheepdogs accounted for approximately 30% of all submissions. The mutant nt230(del4) *MDR1*(−) allele was detected in nine purebred dog breeds, including the Collie, Longhaired Whippet, Shetland Sheepdog, Miniature Australian Shepherd, Australian Shepherd, Wäller, White Swiss Shepherd, Old English Sheepdog, and Border Collie as well as in many herding breed mixes and unclassified mixed breeds (Table 1).

The frequency of the nt230(del4) *MDR1* mutation was highly different between these dog breeds: 81% of all Collies and 75% of all Longhaired Whippets analysed showed at least one mutant *MDR1*(−) allele, which occurred either in the heterozygous *MDR1*(+/−) or the homozygous *MDR1*(−/−) genotype. In Shetland Sheepdogs, Miniature Australian Shepherds, and Australian Shepherds this accounted for 51%, 46%, and 38%, respectively. In the other breeds listed in Table 1, the occurrence of the homozygous mutant *MDR1*(−/−) genotype was rarely detected (White Swiss Shepherd and Border Collie) or was not found in the sample collection (Wäller and Old English Sheepdog).

Although the German Shepherd is a popular dog breed in Germany, only 13 blood samples from this breed were submitted to our laboratory for *MDR1* genotyping. The nt230(del4) *MDR1* mutation was not detected in any of these samples. We received, however, many samples from the White Swiss Shepherd (Berger Blanc Suisse, FCI number 347/1.1) in which the mutant *MDR1*(−) allele occurred with a high allelic frequency of 14%.

Table 2 summarises the *MDR1* genotyping data from nine previous studies worldwide. The frequency data from the present study are similar to the published data for Collies, Australian Shepherds, Miniature Australian Shepherds and Old English Sheepdogs, but the reported frequency from different countries is variable for the Shetland Sheepdog, with allelic frequencies ranging from 1% ($n = 42$) in Japan, 7% ($n = 448$) in the United States, and 36% ($n = 49$) in the United Kingdom. In comparison, the allelic frequency for Shetland Sheepdogs ($n = 960$) was determined to be 30% in the present study.

It was of particular interest to evaluate whether dog breeds that show a close genetic relationship or share a breeding history with one of the predisposed dog breeds are similarly affected by the nt230(del4) *MDR1* mutation. Therefore, dogs from the Bearded Collie, Anatolian Shepherd Dog, Greyhound, Belgian Tervuren, Kelpie, Borzoi, Australian Cattle Dog, and Irish Wolfhound breeds were included in the *MDR1* genotyping analysis. In all of these breeds, however, the nt230(del4) *MDR1* mutation was not detected (Table 3). Of the samples analysed, breed specification was only unclear for one dog that was classified as an Australian Cattle Dog by the owners and showed the heterozygous *MDR1*(+/−) genotype. Although this animal's phenotype clearly corresponded with the typical Australian Cattle Dog breed appearance (documented by photographs), no official pedigree or breeding documents were available and we therefore classified the dog as a mixed breed.

Apart from studying more than 100 purebred dog breeds, we also analysed 379 mixed breed dogs (Table 1); 261 of these showed sheepdog ancestry and 118 were without breed specification. Surprisingly, both cohorts of mixed breed dogs showed high frequencies for the mutant *MDR1*(−) allele, i.e. 8% for the herding breed mixes and 2% for the unclassified mixed breeds.

Discussion

In this study, nine purebred dog breeds were shown to be affected by the nt230(del4) *MDR1* mutation in a large collection of

Table 1
MDR1 genotyping data from 6544 dogs in Germany.

Dog breed	No. of dogs, Σ6544	Allelic frequency (%) *MDR1*(−)	Genotype (%)		
			MDR1(+/+)	*MDR1*(+/−)	*MDR1*(−/−)
Collie[a]	2227	59	19	45	36
Longhaired Whippet	20	45	25	60	15
Shetland Sheepdog	960	30	49	43	8
Miniature Australian Shepherd	72	24	54	43	3
Australian Shepherd	1908	22	62	32	6
Wäller	110	17	65	35	0
White Swiss Shepherd	274	14	75	23	2
Old English Sheepdog	67	4	92	8	0
Border Collie	527	1	98.7	0.9	0.4
Herding breed mix[b]	261	8	86	12	2
Mixed breed[c]	118	2	97	3	0

[a] Dogs classified as American Collie, Longhaired/Rough Collie, Smooth Collie, or Collie were summarised as Collie.
[b] Dogs for which at least one parent was known to be a herding breed (e.g., Collie or Border Collie).
[c] Dogs for which the parentage was either unknown or no parental herding breed was present.

Table 2
Frequency of the *MDR1* genotypes from worldwide genotyping studies.

		US[c]	US[a]	Germany[e]	UK[b]	France[f]	Japan[d]	Germany[g]	UK[a]	North-west US[h]	Australia[i]
Collie	*MDR1*(+/+)	22.6%	26.0%	23.9%	7.1%	20.0%	25.0%	50.0%	14.9%	22.5%	12.1%
	MDR1(+/−)	42.0%	46.0%	43.1%	40.5%	32.0%	33.3%	50.0%	51.1%	42.5%	63.6%
	MDR1(−/−)	35.4%	28.0%	33.0%	52.4%	48.0%	41.7%	0%	34.0%	35.0%	24.3%
	n	*1424*	*161*	*578*	*42*	*25*	*12*	*14*	*94*	*40*	*33*
	AF	*56%*	*51%*	*55%*	*73%*	*64%*	*58%*	*25%*	*60%*	*56%*	*56%*
Shetland Sheepdog	*MDR1*(+/+)	88.2%	84.2%	45.7%	40.8%		97.6%	33.3%			57.1%
	MDR1(+/−)	10.5%	14.7%	48.6%	47.0%		2.4%	0%			42.9%
	MDR1(−/−)	1.3%	1.1%	5.7%	12.2%		0%	66.7%			0%
	n	*448*	*190*	*140*	*49*		*42*	*3*			*7*
	AF	*7%*	*8%*	*30%*	*36%*		*1%*	*67%*			*21%*
Australian Shepherd	*MDR1*(+/+)	53.0%	68.5%	67.9%	32.1%		44.4%	33.3%			35.7%
	MDR1(+/−)	37.0%	29.8%	25.2%	42.9%		44.4%	66.7%			42.8%
	MDR1(−/−)	10.0%	1.7%	6.9%	25.0%		11.2%	0%			21.5%
	n	*1421*	*178*	*333*	*28*		*9*	*3*			*14*
	AF	*29%*	*17%*	*20%*	*46%*		*33%*	*33%*			*43%*
Border Collie	*MDR1*(+/+)	98.4%	100.0%	99.1%	95.3%			87.5%			
	MDR1(+/−)	1.3%	0%	0.6%	4.7%			12.5%			
	MDR1(−/−)	0.3%	0%	0.3%	0%			0%			
	n	*306*	*222*	*334*	*43*			*8*			
	AF	*1%*	*0%*	*1%*	*2%*			*6%*			
Old English Sheepdog	*MDR1*(+/+)	97.5%	92.7%	87.5%	78.8%						
	MDR1(+/−)	2.5%	7.3%	12.5%	21.2%						
	n	*40*	*151*	*24*	*33*						
	AF	*1%*	*4%*	*6%*	*11%*						
Australian Shepherd Miniature	*MDR1*(+/+)	63.1%	51.8%								
	MDR1(+/−)	33.7%	44.6%								
	MDR1(−/−)	3.2%	3.6%								
	n	*285*	*56*								
	AF	*20%*	*26%*								
Longhaired Whippet	*MDR1*(+/+)	41.7%	32.6%								
	MDR1(+/−)	58.3%	51.7%								
	MDR1(−/−)	0%	15.7%								
	n	*24*	*89*								
	AF	*29%*	*42%*								
McNab	*MDR1*(+/+)		68.6%								
	MDR1(+/−)		28.6%								
	MDR1(−/−)		2.8%								
	n		*35*								
	AF		*17%*								
Silken Windhound	*MDR1*(+/+)	68.8%	65.5%								
	MDR1(+/−)	31.2%	33.3%								
	MDR1(−/−)	0%	1.2%								
	n	*16*	*84*								
	AF	*16%*	*18%*								
German Shepherd	*MDR1*(+/+)	89.8%	100.0%								
	MDR1(+/−)	8.4%	0%								
	MDR1(−/−)	1.8%	0%								
	n	*166*	*95*								
	AF	*6%*	*0%*								
English Shepherd	*MDR1*(+/+)	100.0%	85.7%								
	MDR1(+/−)	0%	14.3%								
	n	*28*	*91*								
	AF	*0%*	*7%*								
Wäller	*MDR1*(+/+)			62.9%							
	MDR1(+/−)			37.1%							
	n			*62*							
	AF			*19%*							

Note: *n*, number of dogs analysed; AF, allelic frequency for the mutant *MDR1*(−) allele; a–i, data derived from the following studies:
[a] Neff et al. (2004).
[b] Tappin et al. (2008).
[c] Mealey and Meurs (2008).
[d] Kawabata et al. (2005).
[e] Geyer et al. (2005b).
[f] Hugnet et al. (2004).
[g] Baars et al. (2008).
[h] Mealey et al. (2002).
[i] Mealey et al. (2005).

7378 dogs from Germany. These breeds comprised the Collie, Longhaired Whippet, Shetland Sheepdog, Miniature Australian Shepherd, Australian Shepherd, Wäller, White Swiss Shepherd, Old English Sheepdog, and Border Collie. Furthermore, many mixed

Table 3
Purebred dogs genotyped with *MDR1*(+/+) in different studies worldwide.

Dog breed*	Σ of dogs
Bearded Collie	438[a,b,c,e,g]
Anatolian Shepherd Dog	198[a,b]
Elo	188[b,f]
Greyhound	183[a,b]
Australian Cattle Dog	180[a,b,c]
Labrador Retriever	169[a,b,c,d]
Belgian Tervuren	133[a,b]
Pembroke Welsh Corgi	132[a]
Kelpie	129[a,b]
Italian Greyhound	120[a,b]
Borzoi	114[a,b]
Bernese Mountain	113[a,b]
Flat-Coated Retriever	111[a]
Whippet	105[a]
Jack Russell Terrier	99[a,b]
Shih Tzu	89[a,b,c,d]
Skye Terrier	87[a,b,c]
English Setter	73[a]
Golden Retriever	66[a,b,c,d]
Belgian Malinois	65[a,b]
Belgian Sheepdog	60[a,b]
Koolie	56[a]
Saluki	49[a,b]
Newfoundland	43[a,b]
Beagle	40[a,b]
Weimaraner	39[a,b]
Welsh Sheepdog	37[a]
Dachshund	36[a,b,d]
Icelandic Sheepdog	36[a,b]
Irish Wolfhound	36[b]
Poodle	34[a,b]
Welsh Corgi	34[b,c]
West Highland White Terrier	34[a,b]
Boxer	28[a,b,c]
Cardigan Welsh Corgi	28[a]
Shiba Inu	27[a,d]
Canaan	25[a]
Pug	24[a,b]
Bulldog	22[a,c]
Chinese Shar Pei	22[b]
Rottweiler	22[a,b]
Doberman Pinscher	20[a,b,c]
Rhodesian Ridgeback	20[a,b]
Deerhound	17[b]
Gordon Setter	12[a,b]
Irish Setter	12[a]
Great Dane	12[a,b]
Cavalier King Charles Spaniel	11[a,b]
Heading dog	11[a]
Akabash	10[c]
American Pit Bull Terrier	10[c]
Manchester Terrier	9[a,b]
Norfolk Terrier	9[a]
Scottish Terrier	9[a,b]
Tibetan Terrier	9[a,b]
Dalmatian	8[a,b]
Kerry Blue Terrier	8[a]
Miniature Pinscher	8[a,b]
Saint Bernard	8[a]
Siberian Husky	8[a,b]
Silky Terrier	8[a]
Soft Coated Wheaten Terrier	8[a]
Akita	7[a,b]
Alaskan Malamute	7[a,b]
Basenji	7[a,b]
Border Terrier	7[a]
Cairn Terrier	7[a,b]
Cocker Spaniel, American	7[a,b]
Curly-Coated Retriever	7[a]
English Springer Spaniel	7[a,b]
Finnish Spitz	7[a]
Great Pyrenees	7[a]
Manchester Terrier, Toy	7[a]
Pomeranian	7[a]
Schnauzer, Miniature	7[a]
Vizsla	7[a,b]
American Eskimo	6[a]
American Foxhound	6[a]
American Staffordshire Terrier	6[a]
Bichon Frise	6[a]
Bordeaux Mastiff	6[b]
Boston Terrier	6[a,b]
Brussels Griffon	6[a]
Chow Chow	6[a]
English Cocker Spaniel	6[a]
German Shorthaired Pointer	6[a,b]
German Wirehaired Pointer	6[a,b]
Giant Schnauzer	6[a,b]
Japanese Chin	6[a]
Kuvasz	6[a]
Lowchen	6[a]
Mastiff	6[a,b]
Petit Basset Griffon Vendeen	6[a]
Schnauzer, Standard	6[a]

* Dog breeds were included if at least six dogs were analysed per breed in the following studies:
[a] Neff et al. (2004).
[b] Present study.
[c] Mealey and Meurs (2008).
[d] Kawabata et al. (2005).
[e] Geyer et al. (2005b).
[f] Fecht et al. (2007).
[g] Baars et al. (2008).

breed dogs showed the heterozygous *MDR1*(+/−) and even the homozygous *MDR1*(−/−) mutant genotypes. This outcome was expected because all of these purebred and mixed breed dogs have been shown to be affected by the *MDR1* mutation in previous studies (Neff et al., 2004; Geyer et al., 2005b; Mealey and Meurs, 2008).

It was unexpected to find breeds that show a genetic relationship (Parker et al., 2004) or share a breeding history with one of the predisposed purebred dog breeds (i.e. Bearded Collie, Anatolian Shepherd Dog, Greyhound, Belgian Tervuren, Kelpie, Australian Cattle Dog, Borzoi, and Irish Wolfhound) were free of the *MDR1* mutation. Like a previous study (Neff et al., 2004), a large sample collection was analysed so these breeds are most likely not to be affected by the *MDR1* mutation. This applies in particular to the Bearded Collie, which was re-established in 1949 and is essentially based on working dogs of different origins. Bearded Collies were included in most of the published *MDR1* genotyping studies worldwide and 438 dogs have been tested so far, all with the *MDR1*(+/+) genotype.

It is less clear for the German Shepherd. In a previous study, the nt230(del4) *MDR1* mutation was identified in the White Swiss Shepherd with a high allelic frequency of 13% (Geyer et al., 2007). This study was initiated because of several cases of ivermectin- and doramectin-induced neurotoxicosis among White Swiss Shepherd dogs that were clinically identical with ivermectin-sensitive Collie dogs affected by the nt230(del4) *MDR1* mutation. Based on breeding history, the White Swiss Shepherd is related to the German Shepherd and is not expected to share a Collie ancestry. However, microsatellite analyses showed (Geyer et al., 2007) that White Swiss Shepherd chromosomes carrying the mutant *MDR1*(−) allele exhibited a haplotype that was strongly associated with the mutant *MDR1*(−) allele in breeds of the Collie lineage (Neff et al., 2004). Therefore, White Swiss Shepherd dogs likely acquired the *MDR1* mutation from the Collie lineage by descent (Geyer et al., 2007).

In contrast to Europe (where the White Swiss Shepherd and German Shepherd are independent breed lines) in the US the

White Shepherd is an unacknowledged breed and is generally referred to as the German Shepherd. This might be one reason for the classification of the German Shepherd as a predisposed dog breed for the *MDR1* mutation in US studies (Mealey and Meurs, 2008). Nevertheless, since only a small amount of brown-coloured German Shepherd dogs were analysed for the nt230(del4) *MDR1* mutation in Germany and all were free of this mutation, further *MDR1* genotyping studies are necessary to clarify whether the *MDR1* mutation occurs only in the white or white-factored German Shepherd dogs or even in the brown-coloured ones.

Conclusions

The widespread breed distribution of the nt230(del4) *MDR1* mutation transfers the *MDR1*-related drug sensitivity (first identified in the Collie) to an unpredictable number of individual canine patients. The results should be helpful in providing a first risk estimation for dog breeds that are most likely not affected by this mutation as well as for dog breeds that are definitely affected on the basis of ~15,000 *MDR1* genotyping data from different countries. In the case of the German Shepherd, additional genotyping studies are necessary to evaluate further the occurrence and frequency of the nt230(del4) *MDR1* mutation in this breed.

Conflict of interest statement

MDR1 genotyping is commercially available from TransMIT GmbH, division of Pharmacogenetic Diagnostics PGvet (Professor Joachim Geyer and Professor Ernst Petzinger) at the Institute of Pharmacology and Toxicology, Justus Liebig University of Giessen.

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