

Epidemiology of ocular disorders presumed to be inherited in three small Italian dog breeds in Italy

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Abstract

Objective To describe the prevalence and the types of eye disorders that are known or presumed to be inherited (KP-HED) in three small Italian dog breeds.

Animals Three small Italian dog breeds: Maltese, Bolognese, and Italian Greyhound.

Procedures All dogs of the breeds selected for this prospective observational study that underwent a complete ophthalmic examination between 1994 and 2015 were included. General and proportional KP-HED prevalence with 95% confidence intervals were reported.

Results Three hundred and six of 462 dogs were affected by at least one KP-HED (66.2%; 95% CI: 61.8%–70.4%). In the entire population, the five most common KP-HED were cataract ($n = 122$; rate on the total number of KP-HED: 31.4%), entropion ($n = 56$; 14.4%), keratoconjunctivitis sicca ($n = 33$; 8.5%), retinal dysplasia ($n = 24$; 6.2%), and persistent pupillary membrane (iris to iris) ($n = 21$; 5.4%). The most common KP-HED in each breed were cataracts in the Maltese (35.1%) and in the Bolognese (24.2%), and presentation of vitreous in the anterior chamber in the Italian Greyhound (46.7%).

Conclusions Clinicians should be aware of KP-HED that commonly affect three small Italian dog breeds. Breed standards should be reconsidered, and breeding programs should be directed at limiting such disorders.

Key Words: cataract, hereditary, known and presumed-hereditary eye diseases, PIED, selection, vitreous degeneration

INTRODUCTION

Inherited eye diseases significantly impair vision in humans and animals.^{1–4} As of 2015, 278 genes and loci have been associated with retinal disorders in humans.⁵ The identification and characterization of inherited eye disorders are critical for the diagnosis, prevention, and treatment of such disorders.^{6,7}

Several inherited and presumed to be inherited eye disorders have been described in purebred dogs.^{2,8–11} Until the genetic basis of an ocular disorder is properly defined, ocular disorders that are suspected to have a genetic basis are defined as ‘known and presumed-hereditary eye diseases’ (KP-HED). An ocular disorder is defined as ‘presumed to be inherited’ when 1: it is observed more frequently in one breed compared with other breeds; 2: its incidence increases in a breed; 3: it is observed more

frequently within related dogs of a certain breed; 4: it has a characteristic appearance and location; 5: it has a characteristic age of onset and course of progression; and 6: it is similar to an entity which has been proven to be inherited in other breeds.¹⁰

Italy is homeland of sixteen dog breeds.¹² These include three small-sized breeds: Italian Greyhound [Fédération Cynologique Internationale (FCI) code: 200], which standard has been definitively accepted in 1956 and is included in the group 10, section ‘Short-haired Sighthounds’, Maltese [FCI code: 65], accepted in 1955, and Bolognese [FCI code: 196], accepted in 1956.¹² Both these two latter breeds are included in group 9, ‘Companion and Toy Dogs’ under the section ‘Bichons and related breeds’.¹² Scientific knowledge about KP-HED in these breeds is limited. The 2017 publication of the Hereditary Eye disease (HED) Committee of the ECVO reports data on the

conditions reported in these breeds, but most of the data are based on preliminary reports.¹³ The 2015 official publication of the Genetics Committee of the ACVO presents information on KP-HED for these breeds (including data for 711 Bolognese dogs, 312 Maltese dogs, and 7575 Italian Greyhounds) that are not based on specific publications but on screening examinations or clinical experience of veterinary ophthalmologists.¹⁰ Also, age and sex stratification, which are key epidemiological factors, are not reported. Finally, the Italian Greyhound breed in the USA has sustained significant changes as compared to the original and current Italian breed, as demonstrated by different breed standards.^{14,15}

Therefore, the objective of this study initiated in 1994 is to describe the ophthalmic examination outcomes of these three small Italian dog breeds.

MATERIALS AND METHODS

Study design, outcomes, and animals

Examination findings of three small Italian dog breeds (Maltese, Bolognese, and Italian Greyhounds) were included in this observational study. The primary end point of the present study was to assess the prevalence of KP-HED in these breeds.

Data of Maltese dogs were collected between January 1, 1994, and December 31, 2015, and data of Bolognese dogs and Italian Greyhounds were collected between January 1, 2000, and December 31, 2015. Dogs that presented multiple times were counted as one individual. Ophthalmic examination findings of these three Italian breeds were collected in two different ways: (1) through examinations of presumably healthy individuals for official certification and (2) through ophthalmic examinations of patients presented at different referral veterinary hospitals.

Inclusion criteria

Examination results of all three dog breeds that were scored by a single, board-certified examiner (AG) during the experimental period were included. At dog shows, only purebred dogs, i.e., animals certified with a pedigree document and listed in the Italian Register of Origins (Registro Origini Italiano), were examined and included in the study.

Ophthalmic examination

Each dog included in this study underwent a thorough ocular examination by a boarded ophthalmologist (AG). The examination included the Schirmer tear test (STT—Intervet Inc, NJ, USA), slit-lamp biomicroscopy (SL-5, SL-14, and SL-15 Biomicroscope, Kowa Company Ltd. Japan), direct and indirect ophthalmoscopy (Omega 200 and 500, Heine Optotechnik, Germany), and applanation or rebound tonometry (TonoPen XL; Reichert inc., Depew, NY, USA; TonoVet; Tiolat Oy, Helsinki, Finland). Gonioscopy (18-mm Koeppe lens, Ocular

Instruments Inc., Germany) was only conducted when this test was clinically indicated or explicitly requested by the owner. Applanation tonometry was performed one minute after the application of one drop of topical anesthetic (benoxinate hydrochloride 0.4%, Alfa Intes; Novesina, oxybuprocaine hydrochloride 0.4%, Novartis Farma, Italy). The lens and posterior segment were evaluated 15–20 min after the application of one drop of 1% tropicamide (Visumidriatic, Visufarma, Italy). Once the examination was completed, the results were recorded on an individual certificate.

Classification of ocular disorders

Ocular disorders observed in the dogs were classified as known and presumed-hereditary eye diseases or eye diseases that are not considered inherited. Eye diseases were presumed to be hereditary if they were listed either in the current publication of the Hereditary Eye disease Committee of the ECVO¹³ or the Genetics Committee of the ACVO.¹⁰

After ophthalmic examination, the dogs were categorized as: (1) unaffected: no clinical evidence of any KP-HED or clear clinical evidence that any ocular disorder present was not associated with an inherited condition (e.g., in case of trauma and metabolic conditions); (2) suspicious: presence of specific clinical signs of KP-HED, but lack of clinical certainty; (3) affected: clinical evidence of one or more KP-HED. If the disorder was listed as ‘suspicious’, the owner was advised to present the dog for re-examination within 12 months, depending on the ocular condition.

Statistical analysis

The prevalence of each KP-HED was reported as a function of the total number of the KP-HED and as a function of the total number of animals examined. Furthermore, the prevalence of KP-HED was reported in four age groups: 0–12 months (I), 13–36 months (II), 37–84 months (III), and over 85 months (IV).

Ninety-five percent confidence intervals for a proportion without continuity correction were reported. Bilateral conditions were counted as single events, and multiple conditions in the same eye were counted separately to score prevalence data for each disease. Commercial software was employed for statistical analyses (SPSS; v22.0, SPSS Inc. IBM).

RESULTS

Population and ophthalmic examination

In total, 462 dogs were included in the report. Overall, 267 Maltese, 116 Bolognese, and 79 Italian Greyhounds were examined in the study periods. All the dogs were sexually intact, except for three female Maltese dogs, one female and one male Bolognese dog, and one female Italian Greyhound that were neutered.

Age [mean (range; \pm SD)] of Maltese dogs was 64.3 (2–192; \pm 50.9) months; fifty-seven dogs were in age group I, 54 in age group II, 73 in age group III, and 83 in age group IV. Age of Bolognese dogs was 53.3 (2–204; \pm 42.5) months; twenty-two dogs were in age group I, 33 in age group II, 36 in age group III, and 25 in age group IV. Age of Italian Greyhounds was 68.0 (6–168; \pm 38.0) months; ten dogs were in age group I, 15 in age group II, 34 in age group III, and 20 in age group IV. Of the total, 11 Maltese dogs, 61 Bolognese dogs, and 63 Italian Greyhounds were considered clinically healthy and were presented for official certification examinations.

The number (frequency; 95% confidence interval) of dogs unaffected by KP-HED was 156 (33.8%; 95% CI: 29.61%–38.2%), while 306 dogs were affected by at least one KP-HED (66.2%; 95% CI: 61.8%–70.4%). Of the 267 Maltese examined, 165 (61.8%; 95% CI: 55.8%–67.4%) were diagnosed with a KP-HED, for a total of 191 KP-HED. Of the 116 Bolognese examined, 74 (63.8%; 95% CI: 54.7%–72.0%) were diagnosed with a KP-HED, for a total of 91 KP-HED. Of the 79 Italian Greyhounds examined, 67 (84.8%; 95% CI: 75.3%–91.1%) were diagnosed with a KP-HED, for a total of 107 KP-HED. Stratification of KP-HED by age group is reported in Table 1.

Type of known and presumed-hereditary eye diseases

The type and prevalence of KP-HED are reported in Table 2.

In the entire population, the five most common KP-HED were cataract ($n = 122$; rate on the total number of KP-HED: 31.4%), entropion ($n = 56$; 14.4%), keratoconjunctivitis sicca ($n = 33$; 8.5%), retinal dysplasia ($n = 24$; 6.2%), and persistent pupillary membrane (iris to iris) ($n = 21$; 5.4%).

The five most common KP-HED in the Maltese were cataract ($n = 67$; rate on the number of KP-HED in the breed: 35.1%), medial entropion with trichiasis ($n = 44$; 23.0%), keratoconjunctivitis sicca ($n = 26$; 13.6%), glaucoma ($n = 11$; 5.8%), and prolapsed gland of the third eyelid ($n = 8$; 4.2%).

The five most common KP-HED in the Bolognese were cataract ($n = 22$; 24.2%), persistent pupillary membrane (iris to iris) ($n = 17$; 18.7%), retinal dysplasia ($n = 13$; 14.3%), medial entropion with trichiasis ($n = 11$; 12.1%), and keratoconjunctivitis sicca ($n = 7$; 7.7%).

The five most common KP-HED in the Italian Greyhound were vitreous degeneration with prolapse in the anterior chamber, without any sign of lens luxation ($n = 50$; 46.7%), cataract ($n = 33$; 30.8%), vitreous degeneration (syneresis) ($n = 11$; 10.3%), retinal dysplasia ($n = 4$; 3.7%), and persistent pupillary membrane (iris to iris) ($n = 3$; 2.8%).

Characteristics of cataracts and retinal dysplasia

Of the 267 Maltese dogs, 67 (25.1%) were affected by cataracts and seven (2.6%) by retinal dysplasia. The cataracts were localized as follows: complete (43), posterior subcapsular (6), anterior subcapsular (4), anterior and posterior cortical (3), anterior cortical (3), posterior cortical (2), nuclear (2), posterior suture punctate (1), anterior and posterior subcapsular (1), nuclear and equatorial (1), anterior capsular (1). Of the retinal dysplasia, three were folds, two were geographic, and two were total and associated with retinal detachment.

Of the 116 Bolognese dogs, 22 (19%) were affected by cataracts and 13 (11.2%) by retinal dysplasia. The cataracts were localized as follows: complete (12), anterior subcapsular (2), posterior subcapsular (2), posterior suture punctate (1), anterior cortical (1), anterior and posterior subcapsular (1), nuclear (1), anterior capsular (1), posterior capsular (1). Of the retinal dysplasia, 12 were folds, and one was geographic.

Of the 79 Italian Greyhounds, 33 (41.8%) were affected by cataracts and four (5.1%) by retinal dysplasia. The cataracts were localized as follows: anterior cortical (8), posterior cortical (8), generalized (3), anterior capsular and equatorial (2), anterior cortical and equatorial (2), anterior polar subcapsular (2), anterior sutural (1), posterior cortical (1), anterior and posterior subcapsular (1), nuclear (2), perinuclear (1), posterior capsular (1), anterior and posterior capsular (1). Of the retinal dysplasia, two were folds, and two were geographic.

DISCUSSION

The present study is the first concerning the epidemiological status of KP-HED in small Italian dog breeds in Italy. The present study shows that KP-HED are common in

Table 1. Age distribution in small Italian dog breeds of all KP-HED and selected KP-HED relevant in the specific breed

Age group	Maltese						Bolognese						Greyhound								
	Total	KP-HED		Cataract		Glaucoma		Total	KP-HED		Cataract		Total	KP-HED		Cataract		Vitreous degeneration			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
I	57	40	70.2	2	3.5	0	0	22	17	77.3	0	0	10	4	40	0	0	2		20	
II	54	32	59.3	9	16.7	2	3.7	33	17	51.5	2	6.1	15	11	73.3	0	0	11		73.3	
III	73	46	63	31	42.5	1	1.4	36	19	52.8	7	19.4	34	33	97.1	16	47.1	31		91.2	
IV	83	46	55.4	25	30.1	8	9.6	25	18	72	13	52	20	19	95	17	85	17		85	
Total	267	164	61.4	67	25.1	11	4.1	116	71	61.2	22	19	79	67	84.8	33	41.8	61		77.2	

Age group I: 0–12 months; II: 13–36 months; III: 37–84 months; IV: over 85 months.

Table 2. Type and prevalence of KP-HED in small Italian dog breeds examined during the study time period (1994–2015)

Location	Diagnostic name	Maltese (n = 267)			Bolognese (n = 116)			Italian Greyhound (n = 79)		
		Count	Rate among KP-HED (%)	Prevalence (%)	Count	Rate among KP-HED (%)	Prevalence (%)	Count	Rate among KP-HED (%)	Prevalence (%)
Globe	<i>microphthalmia</i>	4	2.1	1.5						
	<i>glaucoma*</i>	11	5.8	4.1	3	3.3	2.6	2	1.9	2.5
Eyelids	<i>Entropion (trichiasis)</i>	44	23	16.5	11	12.1	9.5	1	0.9	1.3
	<i>distichiasis</i>	1	0.5	0.4				1	0.9	1.3
Nictitans	<i>prolapsed gland of the third eyelid</i>	8	4.2	3	2	2.2	1.7			
Nasolacrimal	<i>KCS</i>	26	13.6	9.7	7	7.7	6			
	<i>imperforate lacrimal punctum</i>				2	2.2	1.7			
Cornea	<i>corneal dystrophy</i>	7	3.7	2.6	2	2.2	1.7			
Uvea	<i>Iris hypoplasia</i>	1	0.5	0.4						
	<i>persistent pupillary membranes, iris to iris</i>	1	0.5	0.4	17	18.7	14.7	3	2.8	3.8
	<i>persistent pupillary membranes, iris to cornea</i>	3	1.6	1.1	1	1.1	0.9			
	<i>iris coloboma</i>	3	1.6	1.1	2	2.2	1.7	1	0.9	1.3
Lens	<i>cataract</i>	67	35.1	25.1	22	24.2	19	33	30.8	41.8
	<i>subluxation/luxation</i>	2	1	0.7	1	1.1	0.9	1	0.9	1.3
Vitreous	<i>vitreous degeneration syneresis</i>							11	10.3	13.9
	<i>vitreous degeneration with prolapse in anterior chamber</i>				2	2.2	1.7	50	46.7	63.3
Retina	<i>retinal dysplasia</i>	7	3.7	2.6	13	14.3	11.2	4	3.7	5.1
	<i>retinal atrophy/PRA</i>	4	2.1	1.5	3	3.3	2.6			
Fundus	<i>coloboma</i>	2	1	0.7						

*All the cases of glaucoma consisted in pectinate ligament anomaly except 1 case in the Italian Greyhound breed that had an open iridocorneal angle.

The rate of KP-HED is calculated as count/total number of KP-HED in the breed and expressed as a percentage. The prevalence is calculated based on the total number of individuals evaluated for each breed.

all three breeds. This report is complementary to the description of KP-HED in three common large Italian dog breeds.¹⁶ The distribution of KP-HED in these three breeds were specific among each breed and different as compared to KP-HED described in other small-sized dog breeds.¹⁷ Three of the five most common KP-HED found in these breeds (i.e., ‘cataract’, ‘keratoconjunctivitis sicca’, ‘retinal dysplasia, geographic or detached forms’) are listed in the current list of the ACVO as ‘disorders for which there is an unequivocal recommendation against breeding in all breeds’.¹⁰

The first most common KP-HED in the population was the cataract. This is not unexpected because cataracts were extremely common also in large Italian dog breeds¹⁶ as well as in other breeds.¹⁸ In a recent survey, on a total of 2739 dogs presented at an ophthalmology referral center in France, 14.7% of them were diagnosed with a cataract.¹⁸ Many reproductive efforts are devoted to limit the spread of this anomaly, but their inefficacy is mostly due to the time of occurrence. In fact, all the Italian Greyhounds affected by cataracts were in the III and IV age group, as well as the majority of the Maltese and Bolognese dogs. Interestingly, on 949 Italian Greyhound

presented to veterinary medical teaching hospitals in North America between 1964 and 2003, 23 were affected by cataracts,¹⁹ resulting in a prevalence of 2.4%, which is much lower than the one observed in our sample. This may be due to several reasons. First, the methods employed to obtain the samples are different, because in the previous study the prevalence was calculated on the total number of Italian Greyhounds presented to North American hospitals independently on whether they underwent an ophthalmic examination.¹⁹ This may have resulted in an underestimation of the number of cataracts. Second, it is possible that the Italian Greyhound breed in other countries has undergone significant breeding pressure, becoming substantially different from the Italian Greyhound breed in Italy.^{14,15}

The second most common KP-HED in the entire population was the medial entropion associated with trichiasis. This syndrome was particularly common in Bolognese and Maltese dogs (23% and 12% of the total of the KP-HED, respectively), while uncommon in Italian Greyhounds. This disorder is probably consequent to alterations of the anatomy of the orbital structures that result in a certain degree of globe protrusion. All the Maltese dogs and 10/11 of the

Bolognese dogs with this disorder were also affected by epiphora. The epiphora associated with medial canthal trichiasis and entropion is a well-described condition, which is considered secondary to the ventral displacement and functional closure of the lower lacrimal punctum and canaliculus, which limits tear drainage.²⁰ We suspect that the high prevalence of this syndrome in Bolognese and Maltese dogs may be a direct consequence of the breed standards that recommend eyes 'larger in size than would be expected, the shape tends to be rounded' and eyes with 'size slightly superior to normal' for Maltese and Bolognese dogs, respectively.^{21,22} As in other breed-related disorders, our findings suggest that a thorough assessment of the impact of these indications on the welfare of the breed is required.²⁰ Finally, a responsible breeding program should be directed toward elimination of these exaggerated facial features.¹⁰

Interestingly, the Italian Greyhounds had quite distinct KP-HED as compared to Maltese and Bolognese breeds. These latter breeds are considered to have a common ancestor,²² and this could partially explain this finding. The most common KP-HED in the Italian Greyhound was the vitreous degeneration, which affected more than three-quarters of the individuals examined. This is in contrast to what was described in the 2015 official publication of the Genetics Committee of the ACVO, where vitreous degeneration was found in approximately one-fifth of the Italian Greyhounds examined.¹⁰ Vitreous degeneration consists in pathological changes of the vitreous body that may lead to syneresis and is sometimes associated with cataracts.²³ None of the Italian Greyhounds evaluated during this period suffered retinal detachment as a consequence of vitreous degeneration or syneresis.²⁴ It is also worth noting that the high prevalence of vitreous degeneration with prolapse into the anterior chamber was not associated with an increase in the prevalence of lens (sub)luxation. Therefore, it is possible that the vitreous humor suffers changes in the fluidity in this breed that result in herniation between intact zonular fibers.

There is some evidence that homozygosity is high in certain Italian Greyhound populations, probably because of nonrandom selection.²⁵ Furthermore, progressive retinal atrophy has been recently proven to be inherited and autosomal recessive in the Italian Greyhound.²⁶ While the high homozygosity may explain the prevalence of disorders observed, the hereditary basis of vitreous degeneration in the Italian Greyhound requires further investigation, because Italy has such a higher prevalence as compared to other countries.¹⁰

As of 2016, 2038 Maltese, 452 Bolognese, and 244 Italian Greyhounds were officially registered in the Italian registry of breeds.¹² Disorders presumed to be inherited are typically associated with breed derivation or with breed bottlenecks. A clear example of this phenomenon is the Irish Wolfhound, a breed with relatively few dogs registered. In the nineteenth century, the Irish Wolfhound

underwent a severe population bottleneck and the breed was thought to be extinct.²² There was a concomitant increase in the incidence of dilated cardiomyopathy in the breed. Indeed, as many as one in three Irish Wolfhounds may be affected by this disorder.²² It is likely that the presence of such a restricted genetic pool is responsible for the observed boost in disease prevalence. The small population size is a concern for the Italian Greyhound and may be one of the factors associated with the high prevalence of KP-HED in this breed.

Although this study is a comprehensive report on the current status of KP-HED in the small Italian breeds, it has some obvious limitations that are related to the lack of proper documentation of most of the KP-HED in the current literature¹⁰ and to its observational design. Data derived from ophthalmology referrals are likely to overestimate certain disorders that are complex to treat and to underestimate other disorders that are easily treated. For example, disorders amenable to surgical repair, such as cataracts, are referred to pertinent centers and could have resulted in an overrepresentation of this disorder in this study. Similarly, disorders, which are easily diagnosed and treated by general practitioners, may be underrepresented in this population. Specifically, the vast majority of the Maltese dogs that were included in this study were patients, rather than dogs that presented for a certifying eye examination. The disease prevalences reported for this breed are therefore more likely to reflect the ones in ophthalmic patients rather than in healthy Maltese dogs.

CONCLUSIONS

The present study fills a gap in veterinary ophthalmic knowledge regarding KP-HED in three Italian small dog breeds in Italy. Each breed has specific KP-HED, and it is likely that many are the consequence of breed recommendations for the shape of the eyes and adnexa. Breed recommendations and consequently breeding efforts should be directed at limiting such disorders.

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