Genetics

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Unusual lecture

Pubmed search “genetic dog, cat”

Pubmed search “candidate gene dog, cat”

+ “retinal disase”

+ “cataract”

And so on…

- Aim to know what is “new” from genetic eye related diseases

- I am not a geneticist,

I am only a clinician in private practice ☺

Optic Nerve

- Assume autosomal recessive with variable but unknown penetrance
- Screened genes can be ruled out as causally associated with the disease

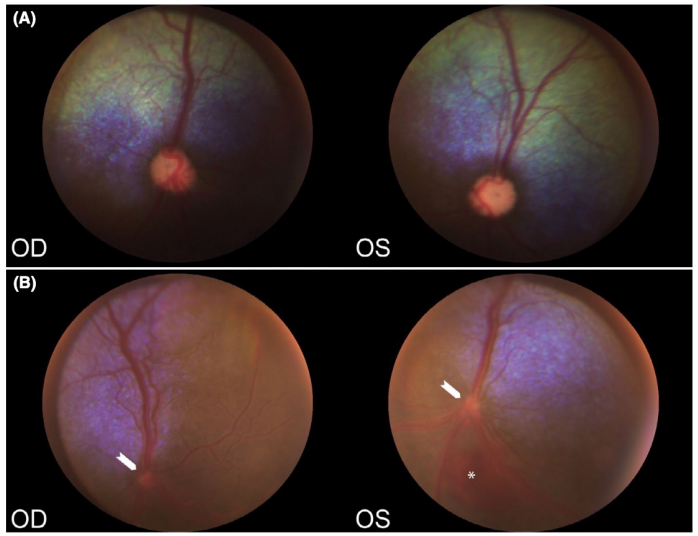

FIGURE 1 Retinal changes in ONH-affected dog. Fundus photographs of two 8-wk-old littermate miniature poodles that are normal (A) or affected with ONH (B) and were included in the pedigree and candidate gene analyses; OD-right eye; OS-left eye. Whereas the normal disk is round, pink, and has a distinct vascular pattern on the surface at 8 wk of age (A), the hypoplastic disks (white arrows) are markedly reduced in size. Note that the ONH-affected OS (B) has a pre-retinal hemorrhage on the retinal surface (asterisk). This is a frequent finding in puppies that arises from bleeding from the regressing hyaloid vasculature and disappears with aging

Optic nerve hypoplasia in miniature poodle dogs: A preliminary genetic and candidate gene association study

Doreen Becker[1,2] | **Jessica K. Niggel**[2] | **Sue Pearce-Kelling**[3] | **Ronald C. Riis**[4] | **Gustavo D. Aguirre**[2]

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Abstract

Objective: To conduct a genetic and candidate gene association study with samples from phenotype-ascertained dogs to identify putative disease-associated gene/mutation for optic nerve hypoplasia (ONH) in the miniature poodle.

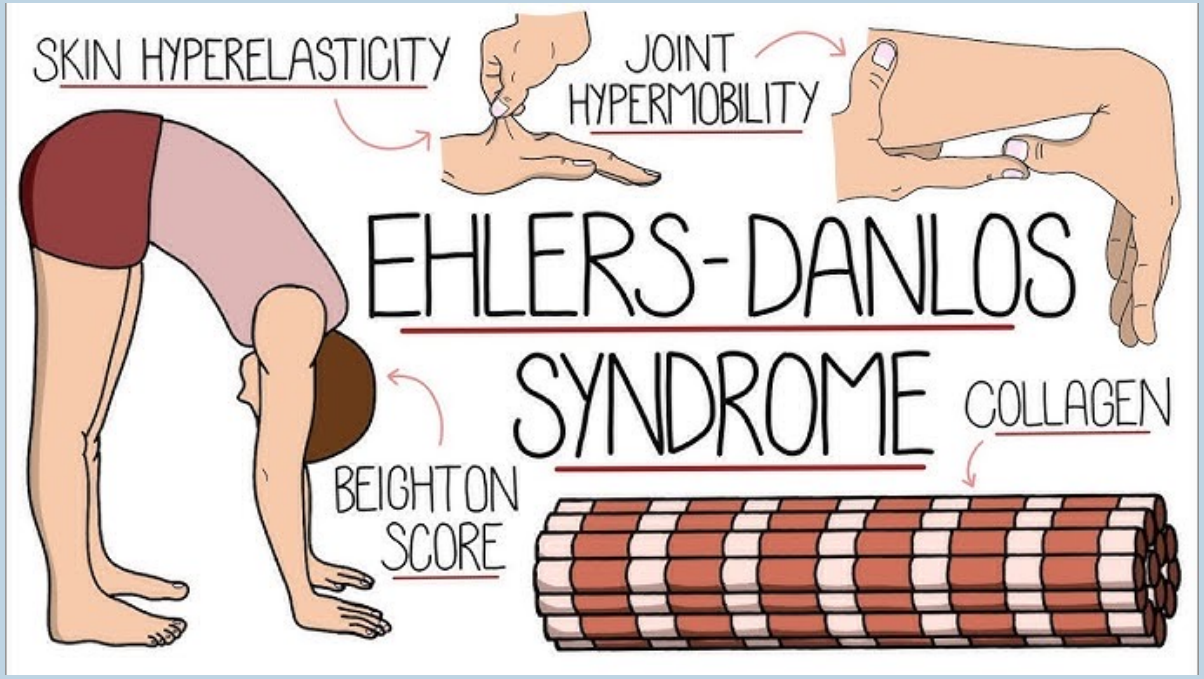
Animals studied: A total of 43 miniature poodles from the United States and Europe, nine affected bilaterally with ONH, were included in the study. Pedigree information was recorded.

Procedures: A pedigree including all animals studied was assembled. Twenty-one genes typically expressed in ganglion cells or that are associated with ocular malformations and have a critical function in eye and neural retina development were selected. Exons and exon-intron boundaries of eight genes were sequenced in four ONH cases and four controls. Furthermore, cases and controls were genotyped with the Illumina CanineHD BeadChip to obtain genotypes for 13 additional candidate genes for haplotype association.

Results: The assembled pedigree connected all ONH-affected dogs to a possible common founder. Identified variants and haplotypes of the tested candidate genes did not segregate with the phenotype using Identity by Descent approach assuming autosomal recessive inheritance with variable but yet unknown penetrance.

Conclusions: Pedigree analysis did not reveal the inheritance pattern. There is no evidence of association of the evaluated candidate genes with ONH; therefore, the screened candidate genes can provisionally be ruled out as causally associated with the disease.

- Ehles-Danlos Syndrome - human:
  - Ocular signs: strabismus, amblyopia, irregular astigmatism, high refractive error, convergence insufficiency, dry eye, spontaneous ectropion, chronic foreign body sensation...
  - General: multiple fractures, stretchy skin, bruising, atrophic scarring, hyperflexible joints, inguinal hernia, exercise intolerante, psychiatric disturbance



Ehlers Danlos Syndrome: An Overview - YouTube

genes

MDPI

Article

Novel Homozygous *ADAMTS2* Variants and Associated Disease Phenotypes in Dogs with Dermatosparactic Ehlers–Danlos Syndrome

Jared A. Jaffey [1,*], Garrett Bullock [2], Juyuan Guo [2], Tendai Mhlanga-Mutangadura [2], Dennis P. O'Brien [3], Joan R. Coates [3], Rochelle Morrissey [4], Robert Hutchison [5], Kevin S. Donnelly [3], Leah A. Cohn [3], Martin L. Katz [6] and Gary S. Johnson [2]

Figure 1. Representative images from two female, 12-week-old, Alapaha Blue Blood Bulldog littermates (Dog 3 (**A**–**C**); Dog 4 (**D**–**F**)) illustrating multifocal wounds at varying stages of healing, atrophic scars, narrowed palpebral fissures, and joint swellings.

- Pit Bull T, Alapaha Blue Blood bulldog – Homozigous variant (n=8)
- Multifocal wounds, atrophic scars, joint hypermobility, narrow palpebral fissures, skin hyperextensibility, joint-associated swellings
- Euthanasia 13 weeks
- Cross sections of collagen fibrils in hieroglyphic-like structures similar to other species with dermatosparaxis
- ADAMTS2 missense mutation

genes

MDPI

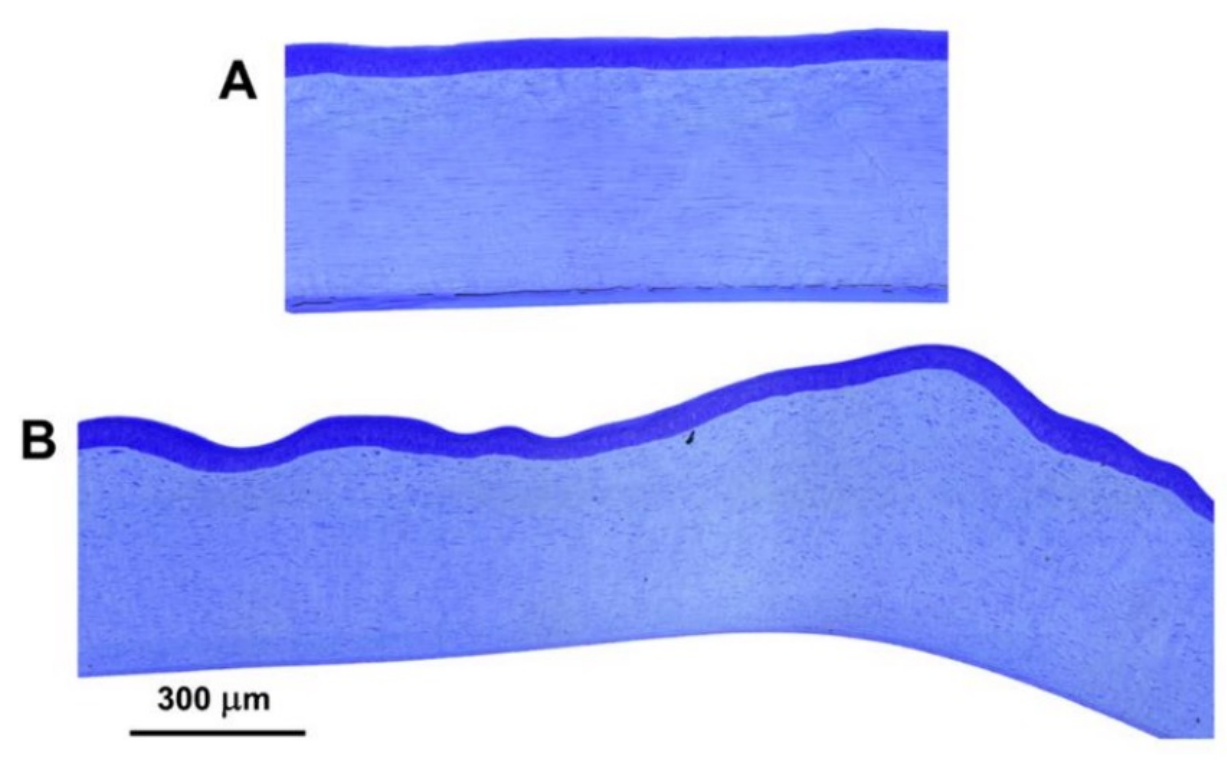
Article

Novel Homozygous *ADAMTS2* Variants and Associated Disease Phenotypes in Dogs with Dermatosparactic Ehlers–Danlos Syndrome

Jared A. Jaffey [1,*], Garrett Bullock [2], Juyuan Guo [2], Tendai Mhlanga-Mutangadura [2], Dennis P. O'Brien [3], Joan R. Coates [3], Rochelle Morrissey [4], Robert Hutchison [5], Kevin S. Donnelly [3], Leah A. Cohn [3], Martin L. Katz [6]

Figure 7. Representative images from a Catahoula Leopard dog illustrating normal palpebral fissures (**A**), hyperextensible skin (**B**), sagging skin (**C**,**D**), typical wounds (**E**,**F**), joint hypermobility (**G**), and atrophic scars (**H**).

. Topography irregular
- Normal corneal thickness
- Descemets membrane much thinner



- Diameters of fibrils similar
- Boundaries of the fibrils less distinct
- Packing of the collagen was looser and less regular than affected dogs

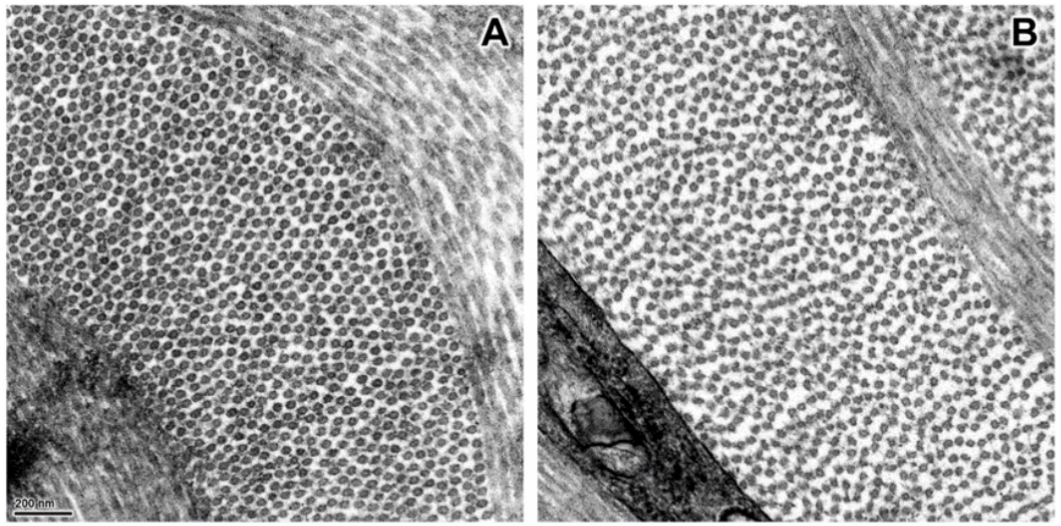
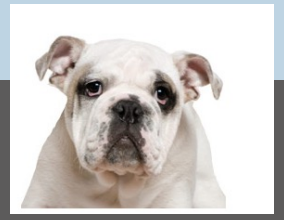
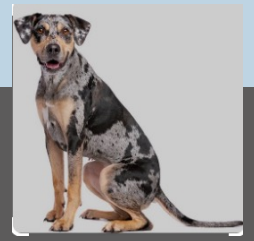


Figure 6. Electron micrographs of cross sections of collagen fibrils from the corneas of an unaffected 10.5-month-old Dachshund (**A**) and from one of the affected Alapaha Blue Blood Bulldog puppies (**B**). In the normal cornea, the collagen fibrils were circular in profile and quite uniform in diameter. The diameters of the corneal collagen fibrils from the affected dogs were similar to those of the normal cornea, but their boundaries were less distinct, and their profiles were more variable. In addition, the packing of the collagen fibrils of the affected dog corneas was looser and less regular than in the cornea from the unaffected dog.

Table 1. Molecular-genetic and clinical features of dogs with dermatosparactic Ehlers-Danlos Syndrome.

Dog Identity	Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6	Dog 7	Dog 8
reed	Pit Bull Terrier	Pit Bull Terrier	Alapaha Blue Blood Bulldog	Alapaha Blue Blood Bulldog	Alapaha Blue Blood Bulldog	Alapaha Blue Blood Bulldog	Catahoula Leopard Dog	Doberman Pinscher
Mutation	11:2280117delC	11:2280117delC	11:2280117delC	11:2280117delC	11:2280117delC	11:2280117delC	11:2491238G>A	11:2408978C>T
Mutation type	Frameshift	Frameshift	Frameshift	Frameshift	Frameshift	Frameshift	Missense	Nonsense
Mutation zygosity	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous
Euthanasia	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Age at death	8 Weeks	8 Weeks	12 Weeks	12 Weeks	8 Weeks	8 Weeks	>9 Years	8 Weeks
Fragile skin	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Atrophic scars	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hyper-extensible Skin	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Joint instability	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Swollen joints	Yes	No	Yes	Yes	Yes	Yes	Infrequent	Yes
Periocular lesions	Micropalpebral fissures	None	Micropalpebral fissures	Micropalpebral fissures	Micropalpebral fissures	Micropalpebral fissures	None	Ocular Chemosis
Ataxia	Yes	No	No	Yes	No	No	No	No





Cataracts

- FYCO1 candidate causative variant juvenile cataract

Article

FYCO1 Frameshift Deletion in Wirehaired Pointing Griffon Dogs with Juvenile Cataract

Gabriela Rudd Garces [1,2], Matthias Christen [1], Robert Loechel [3], Vidhya Jagannathan [1] and Tosso Leeb [1,*]

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Abstract: Different breed-specific inherited cataracts have been described in dogs. In this study, we investigated an inbred family of Wirehaired Pointing Griffon dogs in which three offspring were affected by juvenile cataract. The pedigree suggested monogenic autosomal recessive inheritance of the trait. Whole-genome sequencing of an affected dog revealed 12 protein-changing variants that were not present in 566 control genomes, of which two were located in functional candidate genes, *FYCO1* and *CRYGB*. Targeted genotyping of both variants in the investigated family excluded *CRYGB* and revealed perfect co-segregation of the *FYCO1* variant with the juvenile cataract phenotype. This variant, *FYCO1*:c.2024delG, represents a 1 bp frameshift deletion predicted to truncate ~50% of the open reading frame p.(Ser675Thrfs*5). *FYCO1* encodes the FYVE and coiled-coil domain autophagy adaptor 1, a known regulator of lens autophagy, which is required for the normal homeostasis in the eye. In humans, at least 37 pathogenic variants in *FYCO1* have been shown to cause autosomal recessive cataract. *Fcyo1*$^{-/-}$ knockout mice also develop cataracts. Together with the current knowledge on *FYCO1* variants and their functional impact in humans and mice, our data strongly suggest *FYCO1*:c.2024delG as a candidate causative variant for the observed juvenile cataract in Wirehaired Pointing Griffon dogs. To the best of our knowledge, this study represents the first report of a *FYCO1*-related cataract in domestic animals.

Keywords: *Canis lupus familiaris*; whole-genome sequence; ophthalmology; lens; animal model; precision medicine; veterinary medicine

check for updates

Citation: Rudd Garces, G.; Christen, M.; Loechel, R.; Jagannathan, V.; Leeb, T. *FYCO1* Frameshift Deletion in Wirehaired Pointing Griffon Dogs with Juvenile Cataract. *Genes* **2022**, *13*, 334. https://doi.org/10.3390/genes13020334

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- CFA20 and CFA21 two loci associated with PPC – possibly dominant
- CFA4 and CFA30 close proximity to cataract candidate gene

RESEARCH Open Access

Cataracts in Havanese: genome wide association study reveals two loci associated with posterior polar cataract

Kim K. L. Bellamy[1,2*] and Frode Lingaas[2]

Abstract

Background Cataract is considered an important health issue in Havanese, and studies indicate a breed predisposition. Possible consequences of cataracts include lens induced uveitis, reduced eyesight, and blindness in severe cases. Reducing the prevalence of cataracts could therefore improve health and welfare significantly. The most frequently diagnosed forms of cataract in Havanese are cortical- and anterior suture line cataract, but cases of posterior polar cataract are also regularly reported. Out of the three, posterior polar- and cortical cataracts are considered the most clinically relevant.

Results We performed a genome wide association study that included 57 controls and 27 + 23 + 7 cases of cortical-, anterior suture line- and posterior polar cataract, respectively. An association analysis using a mixed linear model, revealed two SNPs on CFA20 (BICF2S23632983, $p = 7.2e-09$) and CFA21 (BICF2G630640490, $p = 3.3e-09$), that were significantly associated with posterior polar cataract, both of which are linked to relevant candidate genes. The results suggest that the two variants are linked to alleles with large effects on posterior polar cataract formation, possibly in a dominant fashion, and identifies regions that should be subject to further sequencing.

Promising regions on CFA4 and CF30 were also identified in the association analysis of cortical cataract. The top SNPs on each chromosome, chr4_12164500 ($p = 4.3e-06$) and chr30_28836339 ($p = 5.6e-06$), are located within, or in immediate proximity to, potential cataract candidate genes.

The study shows that age at examination is strongly associated with sensitivity of cataract screening. Havanese in Norway are on average 3.4 years old when eye examinations are performed: an age where most dogs that are genetically at risk have not yet developed clinically observable changes. Increasing the average age of breeding animals could increase accuracy of selection, leading to improved health.

Conclusions The study identified two loci, on CFA20 and CFA21, that were significantly associated with posterior polar cataract in Havanese. SNPs that showed putative association with cortical cataracts, were observed on CFA4 and CFA30. All the top SNPs are located in close proximity to cataract candidate genes. The study also show that sensitivity of cataract screening is highly dependent on age at examination.

Keywords GWAS, Cataract, Havanese, ECVO, *ANO3*, *FOXP1*, *RYBP*, *LGR4*, *ANK3*, *PCLAF*

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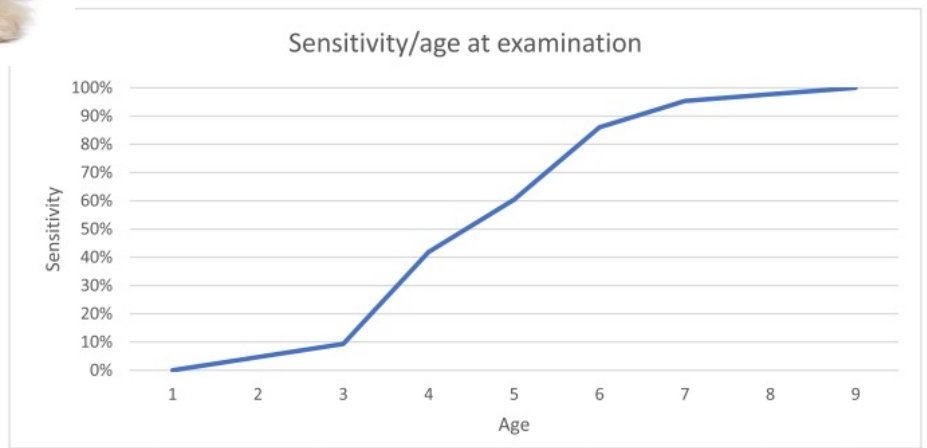
[2] Department of Preclinical Sciences and Pathology, Faculty of Veterinary Medicine, Norwegian University of Life Sciences, Ås, Norway

Background

Cataract is considered an important health challenge in the Havanese dog breed [1], and is characterized by opacities of the lens [2]. Approximately 5% of ECVO eye examinations of Havanese in Norway result in a cataract

- CFA20 and CFA21 two loci associated with PPC – possibly dominant
- CFA4 and CFA30 close proximity to cataract candidate gene
- Sensitivity of cataract screening highly dependent on age at examination



Age at examination	1	2	3	4	5	6	7	8	9
Sensitivity	-	0.05	0.09	0.42	0.60	0.86	0.95	0.98	1.00
95% CI		[0.00, 0.11]	[0.01, 0.18]	[0.27, 0.57]	[0.46, 0.75]	[0.76, 0.96]	[0.89, 1.00]	[0.93, 1.00]	

Fig. 2 Sensitivity at different ages at examination. Estimated from 43 Havanese in the dataset that had been diagnosed with cataracts within two years after a negative diagnosis

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A defect in the *NOG* gene increases susceptibility to spontaneous superficial chronic corneal epithelial defects (SCCED) in boxer dogs

Kathryn M. Meurs,[1,2] Keith Montgomery,[1,2] Steven G. Friedenberg,[3] Brian Williams,[1,2] and Brian C. Gilger[1,2]

Abstract

Go to:

Background

Superficial chronic corneal epithelial defects (SCCEDs) are spontaneous corneal defects in dogs that share many clinical and pathologic characteristics to recurrent corneal erosions (RCE) in humans. Boxer dogs are predisposed to SCCEDs, therefore a search for a genetic defect was performed to explain this susceptibility. DNA was extracted from blood collected from Boxer dogs with and without SCCEDs followed by whole genome sequencing (WGS). RNA sequencing of corneal tissue and immunostaining of corneal sections from affected SCCED Boxer dogs with a deletion in the *NOG* gene and affected non-Boxer dogs without the deletion were performed.

Results

A 30 base pair deletion at a splice site in Noggin (*NOG*) (Chr 9:31453999) was identified by WGS and was significantly associated ($P < 0.0001$) with Boxer SCCEDs compared to unaffected non-Boxer dogs. NOG, BMP4, MMP13, and NCAM1 all had significant fold reductions in expression and SHH was significantly increased in Boxers with the *NOG* deletion as identified by RNA-Seq. Corneal IHC from *NOG* deletion dogs with SCCEDs had lower NOG and significantly higher scores of BMP2.

Conclusions

Many Boxer dogs with SCCED have a genetic defect in *NOG*. *NOG* is a constitutive protein in the cornea which is a potent inhibitor of BMP, which likely regulate limbal epithelial progenitor cells (LEPC). Dysregulation of LEPC may play a role in the pathogenesis of RCE.

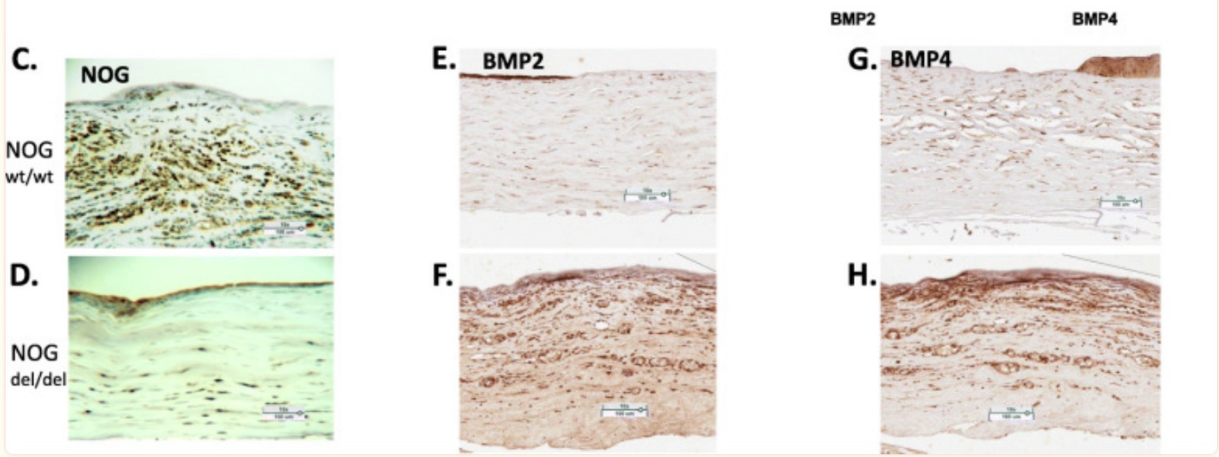

Fig. 2

Immunohistochemistry (IHC) Scores of Keratectomy Specimens of Dogs with Chronic non-healing Corneal ulcers (Scatterplot, median). **A** NOG staining. Samples from NOG del/del dogs had a lower mean NOG IHC score than samples from NOG wt/wt, but the difference was not significant ($p = 0.0625$). **B** BMP2, and 4 IHC scores of samples from NOG del/del and NOG wt/wt dogs. Keratectomy specimens from NOG del/del dogs had significantly higher BMP2 ($p = 0.008$) than samples from NOG wt/wt dogs (Man Whitney U Test). Representative IHC images of keratectomy samples from NOG wt/wt and NOG del/del dogs. C. NOG score 3; D. NOG score 1; E. BMP2 score 1; F. BMP2 score 3; G.BMP4 score 1; H. BMP 4 score 3. 10X Magnification

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Genetic prevalence and clinical relevance of canine Mendelian disease variants in over one million dogs

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Genetic prevalence and clinical relevance of canine Mendelian disease variants in over one million dogs

- **Allele frequency** refers to how common a specific allele (a version of a gene) is in a population
- In genetics, an allele is one of two or more versions of a gene. For example, a gene may exist in two forms, one causing a certain disease and another being normal

Table 1

Putative disease-associated variants with allele frequency >0.5% in the examined canine population.

OMIA variant ID[1]	Variant phenotype	Mode of inheritance	Gene	Variant[2]	Allele frequenc all dogs [%]	Allele frequenc mixed breed dogs [%]	Allele frequency purebred dogs [%]
855	Chondrodystrophy and Intervertebral Disc Disease Risk (CDDY)	Autosomal dominant	*FGF4*	chr12:33710178ins	11.951	11.353	13.945
36	Degenerative Myelopathy (DM)	Autosomal recessive (Incomplete penetrance)	*SOD1*	chr31:26540342G>A	7.858	7.506	9.037
699	Cone-Rod Dystrophy (cord1-PRA/crd4)	Autosomal recessive (Incomplete penetrance)	*RPGRIP1*	chr15:18332036_18332037ins[A [29];GGAAGCAACAGGATG]	3.809	3.641	4.370
76	Progressive Rod-Cone	Autosomal recessive	*PRCD*	chr9:4188663C>T	2.923	3.314	1.613

Disease-associated variants found in additional breeds at an allele frequency ≥1%

Variant phenotype	Mode of inheritance	Gene	Variant[2]	Previously identified breed(s)	Additional identified breeds (Total N dogs screened; Variant frequency)
Primary Lens Luxation (PLL)	Autosomal recessive	*ADAMTS17*	chr3:40782144G>A	>30	Coyote (9; 16.67%) McNab (28; 7.14%) Scottish Terrier (237; 1.05%)
Bardet-Biedl syndrome 2 or Progressive Retinal Atrophy (Discovered in the Shetland Sheepdog; BBS2-PRA)	Autosomal recessive	*BBS2*	chr2:59693737G>C	Shetland Sheepdog	Miniature American Shepherd (1476; 1.36%)
Progressive Rod-Cone	Autosomal	*PRCD*	chr9:4188663C>T	>50	Bichon Frise
Microphthalmia (Discovered in the Soft-Coated Wheaten Terrier)	Autosomal recessive	*RBP4*	chr28:7830265_7830267del	Irish Soft-Coated Wheaten Terrier	Russell Terrier (239; 6.49%)
Neuronal Ceroid Lipofuscinosis 8 (Discovered in the English Setter; NCL8)	Autosomal recessive	*CLN8*	chr37:30874779T>C	English Setter	Gordon Setter (20; 5%)

Disease-associated variants found in additional breeds at an allele frequency ≥1%

Variant phenotype	Mode of inheritance	Gene	Variant[2]	Previously identified breed(s)	Additional identified breeds (Total N dogs screened; Variant frequency)
Collie Eye Anomaly (CEA)	Autosomal recessive	*NHEJ1*	chr37:25698028_25705826del	>10	Anatolian Shepherd Dog (66; 3.79%) Lacy Dog (32: 9.38%)
Canine Multifocal Retinopathy 1 (Discovered in Mastiff-related breeds; CMR1)	Autosomal recessive	*BEST1*	chr18:54478586G>A	Boerboel, Bull Mastiff, English Mastiff, Great Pyrenees	Boston Terrier (3702; 7.47%) Neapolitan Mastiff (90; 1.11%)
Ehlers-Danlos Syndrome (Discovered in the Chihuahua and Poodle)	Autosomal recessive	*TNXB*	chr12:1490385G>A	Chihuahua, Poodle	German Pinscher (13; 38.46%) German Shorthaired Pointer (65; 2.31%) Pomeranian (121; 4.55%)

RESEARCH ARTICLE

A Naturally Occurring Canine Model of Autosomal Recessive Congenital Stationary Night Blindness

Mineo Kondo[1]*, Gautami Das[2], Ryoetsu Imai[3], Evelyn Santana[2], Tomio Nakashita[3], Miho Imawaka[3], Kosuke Ueda[3], Hirohiko Ohtsuka[3], Kazuhiko Sakai[4], Takehiro Aihara[4], Kumiko Kato[1], Masahiko Sugimoto[1], Shinji Ueno[5], Yuji Nishizawa[6], Gustavo D. Aguirre[2]*, Keiko Miyadera[2]

Abstract

Congenital stationary night blindness (CSNB) is a non-progressive, clinically and genetically heterogeneous disease of impaired night vision. We report a naturally-occurring, stationary, autosomal recessive phenotype in beagle dogs with normal daylight vision but absent night vision. Affected dogs had normal retinas on clinical examination, but showed no detectable rod responses. They had "negative-type" mixed rod and cone responses in full-field ERGs. Their photopic long-flash ERGs had normal OFF-responses associated with severely reduced ON-responses. The phenotype is similar to the Schubert-Bornschein form of complete CSNB in humans. Homozygosity mapping ruled out most known CSNB candidates as well as *CACNA2D4* and *GNB3*. Three remaining genes were excluded based on sequencing the open reading frame and intron-exon boundaries (*RHO*, *NYX*), causal to a different form of CSNB (*RHO*) or X-chromosome (*NYX*, *CACNA1F*) location. Among the genes expressed in the photoreceptors and their synaptic terminals, and mGluR6 cascade and modulators, reduced expression of *GNAT1*, *CACNA2D4* and *NYX* was observed by qRT-PCR in both carrier (n = 2) and affected (n = 2) retinas whereas *CACNA1F* was down-regulated only in the affecteds. Retinal morphology revealed normal cellular layers and structure, and electron microscopy showed normal rod spherules and synaptic ribbons. No difference from normal was observed by immunohistochemistry (IHC) for antibodies labeling rods, cones and their presynaptic terminals. None of the retinas showed any sign of stress. Selected proteins of mGluR6 cascade and its modulators were examined by IHC and showed that PKCα weakly labeled the rod bipolar somata in the affected, but intensely labeled axonal terminals that appeared thickened and irregular. Dendritic terminals of ON-bipolar cells showed increased Goα labeling. Both PKCα and Goα labeled the more prominent bipolar dendrites that extended into the OPL in affected but not normal retinas. Interestingly, RGS11 showed no labeling in the affected retina. Our results indicate involvement of a yet unknown gene in this canine model of complete CSNB.

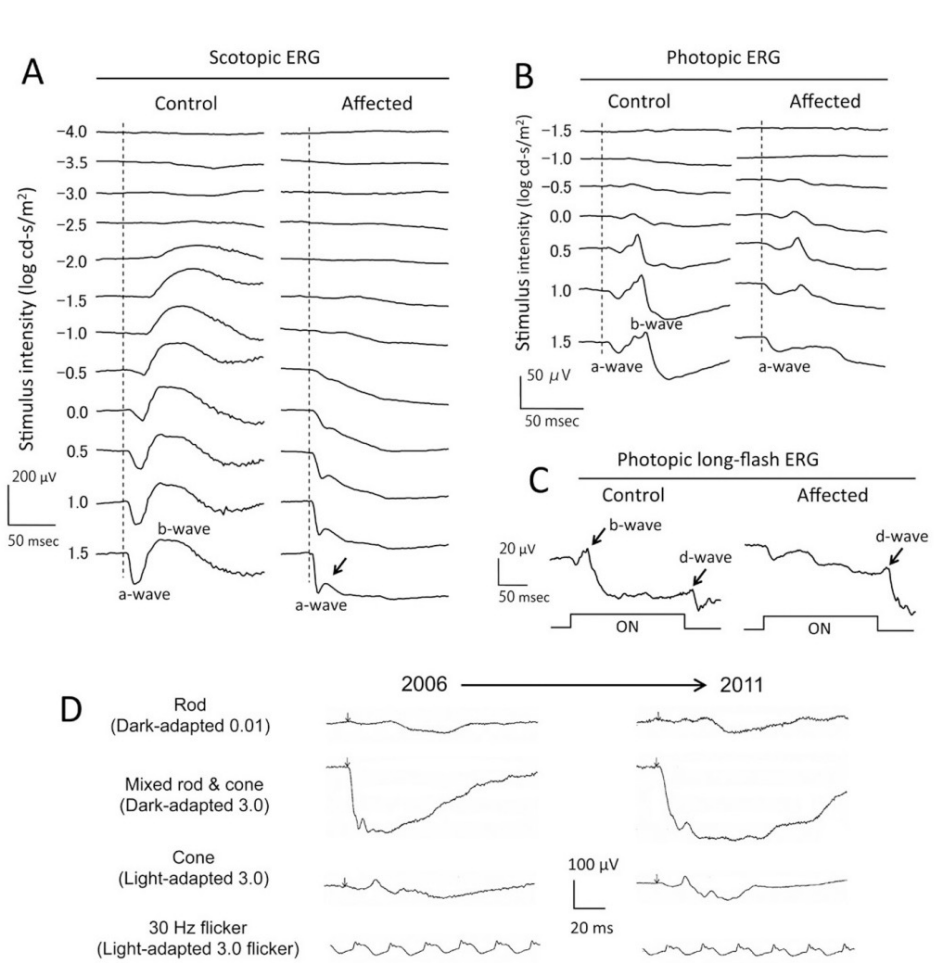


Fig 3. Scotopic and photopic ERGs show a defect in signal transmission from rods and cones to ON-bipolar cells. Electroretinograms (ERGs) recorded from CSNB dogs. **A**) Dark-adapted (scotopic) ERGs elicited by different stimulus intensities. Affected dog shows normal a-wave but loss of the b-wave. **B**) Light-adapted (photopic) ERGs elicited by different stimulus intensities. Affected dog shows a reduction of the b-wave at higher stimulus intensities of 1.0–1.5 log cd-s/m^2. **C**) Photopic long-flash ERG using 200 ms stimuli of 400 cd/m^2. Affected dog shows reduced ON-response (b-wave), but normal OFF-response (d-wave). **D**) Standard ERGs recommended by ISCEV [70] recorded from the same affected dog at 2 and 7years-of-age showed no progressive ERG changes in the 5 year interval.

doi:10.1371/journal.pone.0137072.g003

- CSNB: clinically and genetically heterogeneous disease
- Night vision impairment
- Naturally occuring
- Retinal morphology no changes:
  - Normal cellular layers and structure
  - Normal rod spherules and synaptic ribbons
  - No signs of stress
  - Dendritic terminals of ON-bipolar that extended into the OPL
  - Involvement of RGS11 - no labelling in the affected retina

RESEARCH ARTICLE

A Naturally Occurring Canine Model of Autosomal Recessive Congenital Stationary Night Blindness

Mineo Kondo[1]*, Gautami Das[2], Ryoetsu Imai[3], Evelyn Santana[2], Tomio Nakashita[3], Miho Imawaka[3], Kosuke Ueda[3], Hirohiko Ohtsuka[3], Kazuhiko Sakai[4], Takehiro Aihara[4], Kumiko Kato[1], Masahiko Sugimoto[1], Shinji Ueno[5], Yuji Nishizawa[6], Gustavo D. Aguirre[2]*, Keiko Miyadera[2]

Abstract

Congenital stationary night blindness (CSNB) is a non-progressive, clinically and genetically heterogeneous disease of impaired night vision. We report a naturally-occurring, stationary, autosomal recessive phenotype in beagle dogs with normal daylight vision but absent night vision. Affected dogs had normal retinas on clinical examination, but showed no detectable rod responses. They had "negative-type" mixed rod and cone responses in full-field ERGs. Their photopic long-flash ERGs had normal OFF-responses associated with severely reduced ON-responses. The phenotype is similar to the Schubert-Bornschein form of complete CSNB in humans. Homozygosity mapping ruled out most known CSNB candidates as well as *CACNA2D4* and *GNB3*. Three remaining genes were excluded based on sequencing the open reading frame and intron-exon boundaries (*RHO*, *NYX*), causal to a different form of CSNB (*RHO*) or X-chromosome (*NYX*, *CACNA1F*) location. Among the genes expressed in the photoreceptors and their synaptic terminals, and mGluR6 cascade and modulators, reduced expression of *GNAT1*, *CACNA2D4* and *NYX* was observed by qRT-PCR in both carrier (n = 2) and affected (n = 2) retinas whereas *CACNA1F* was down-regulated only in the affecteds. Retinal morphology revealed normal cellular layers and structure, and electron microscopy showed normal rod spherules and synaptic ribbons. No difference from normal was observed by immunohistochemistry (IHC) for antibodies labeling rods, cones and their presynaptic terminals. None of the retinas showed any sign of stress. Selected proteins of mGluR6 cascade and its modulators were examined by IHC and showed that PKCα weakly labeled the rod bipolar somata in the affected, but intensely labeled axonal terminals that appeared thickened and irregular. Dendritic terminals of ON-bipolar cells showed increased Goα labeling. Both PKCα and Goα labeled the more prominent bipolar dendrites that extended into the OPL in affected but not normal retinas. Interestingly, RGS11 showed no labeling in the affected retina. Our results indicate involvement of a yet unknown gene in this canine model of complete CSNB.

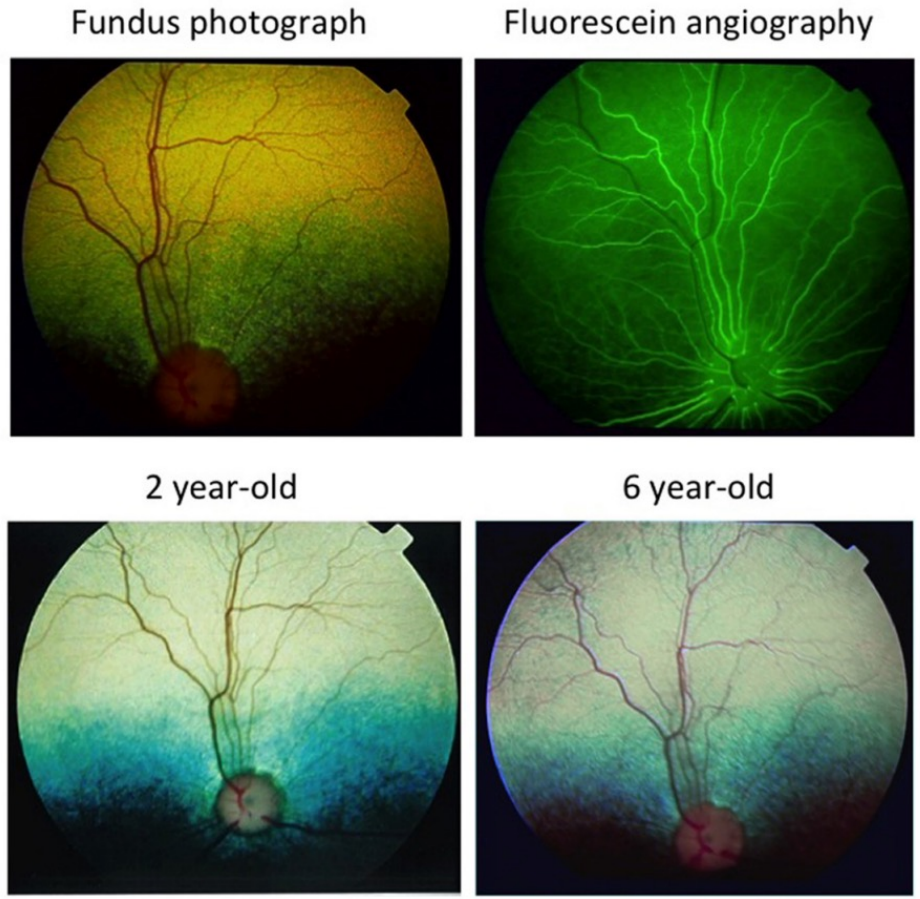
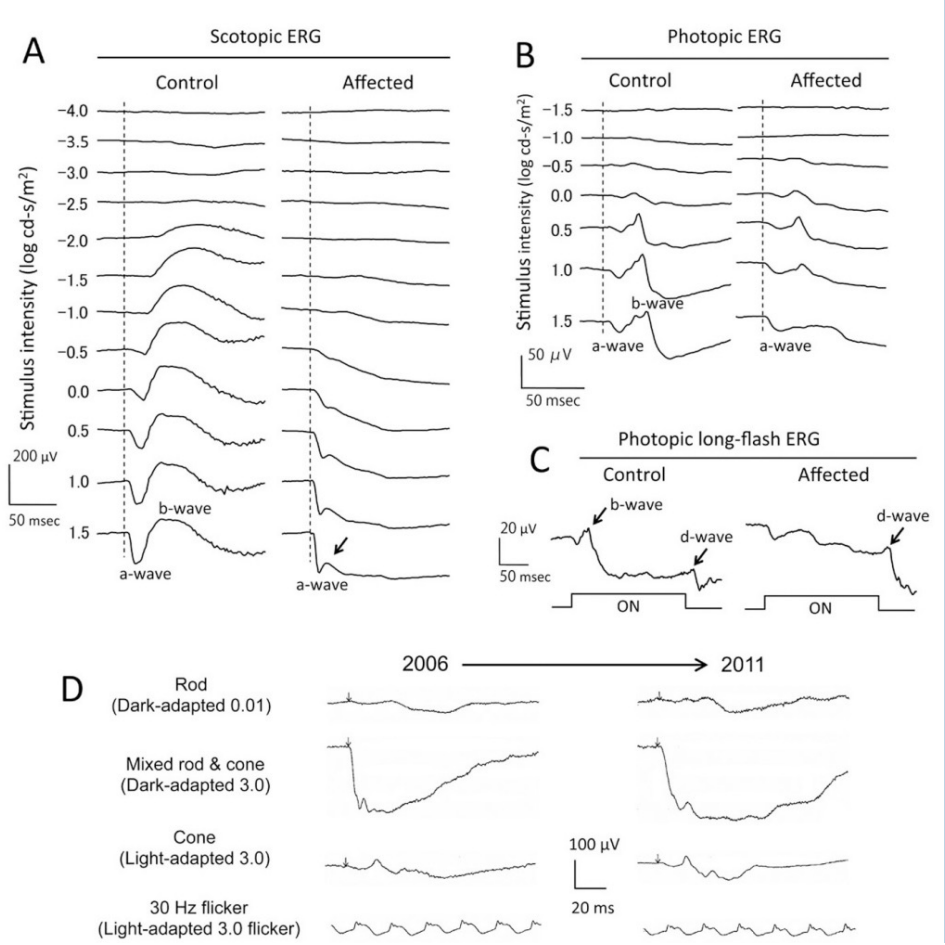


Fig 2. Retinal examination shows no abnormalities over time. Fundus photographs of the same dog show normal retinal integrity and vasculature. The tapetal retina (green-yellow color above the optic disc) shows a different color in the photographs due to the different light intensities used. The retina remains normal and unchanged during a 4 year observation period. The fluorescein angiogram (top right) shows normal vascular perfusion during the late arteriolar phase; the venules are just beginning to fill with contrast.



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RESEARCH ARTICLE Open Access

A LINE-1 insertion situated in the promoter of *IMPG2* is associated with autosomal recessive progressive retinal atrophy in Lhasa Apso dogs

Rebekkah J. Hitti-Malin[1,2*], Louise M. Burmeister[1], Sally L. Ricketts[1], Thomas W. Lewis[3,4], Louise Pettitt[1], Mike Boursnell[1], Ellen C. Schofield[1], David Sargan[2] and Cathryn S. Mellersh[1]

Abstract

Background: Canine progressive retinal atrophies are a group of hereditary retinal degenerations in dogs characterised by depletion of photoreceptor cells in the retina, which ultimately leads to blindness. PRA in the Lhasa Apso (LA) dog has not previously been clinically characterised or described in the literature, but owners in the UK are advised to have their dog examined through the British Veterinary Association/ Kennel Club/ International Sheep Dog Society (BVA/KC/ISDS) eye scheme annually, and similar schemes that are in operation in other countries. After the exclusion of 25 previously reported canine retinal mutations in LA PRA-affected dogs, we sought to identify the genetic cause of PRA in this breed.

Results: Analysis of whole-exome sequencing data of three PRA-affected LA and three LA without signs of PRA did not identify any exonic or splice site variants, suggesting the causal variant was non-exonic. We subsequently undertook a genome-wide association study (GWAS), which identified a 1.3 Mb disease-associated region on canine chromosome 33, followed by whole-genome sequencing analysis that revealed a long interspersed element-1 (LINE-1) insertion upstream of the *IMPG2* gene. *IMPG2* has previously been implicated in human retinal disease; however, until now no canine PRAs have been associated with this gene. The identification of this PRA-associated variant has enabled the development of a DNA test for this form of PRA in the breed, here termed PRA4 to distinguish it from other forms of PRA described in other breeds. This test has been used to determine the genotypes of over 900 LA dogs. A large cohort of genotyped dogs was used to estimate the allele frequency as between 0.07–0.1 in the UK LA population.

(Continued on next page)

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Conclusions: Through the use of GWAS and subsequent sequencing of a PRA case, we have identified a LINE-1 insertion in the retinal candidate gene *IMPG2* that is associated with a form of PRA in the LA dog. Validation of this variant in 447 dogs of 123 breeds determined it was private to LA dogs. We envisage that, over time, the developed DNA test will offer breeders the opportunity to avoid producing dogs affected with this form of PRA.

Keywords: Canine, Dog, Progressive retinal atrophy, PRA, Canine retinal degeneration, Inherited, Photoreceptor degeneration, *IMPG2*

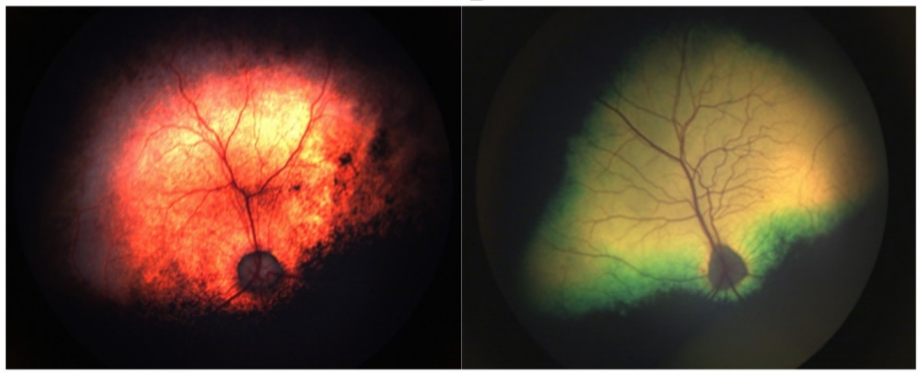


Fig. 6 Fundus changes observed in a LA with PRA. **a** An image of the retina in the left eye of a PRA4 $^{-/-}$ LA dog. Bilateral tapetal hyperreflectivity was observed as well as mild vascular attenuation and changes to the optic disc colouration. **b** An image of the retina of a control dog (Giant Schnauzer dog) with a normal fundus [30]

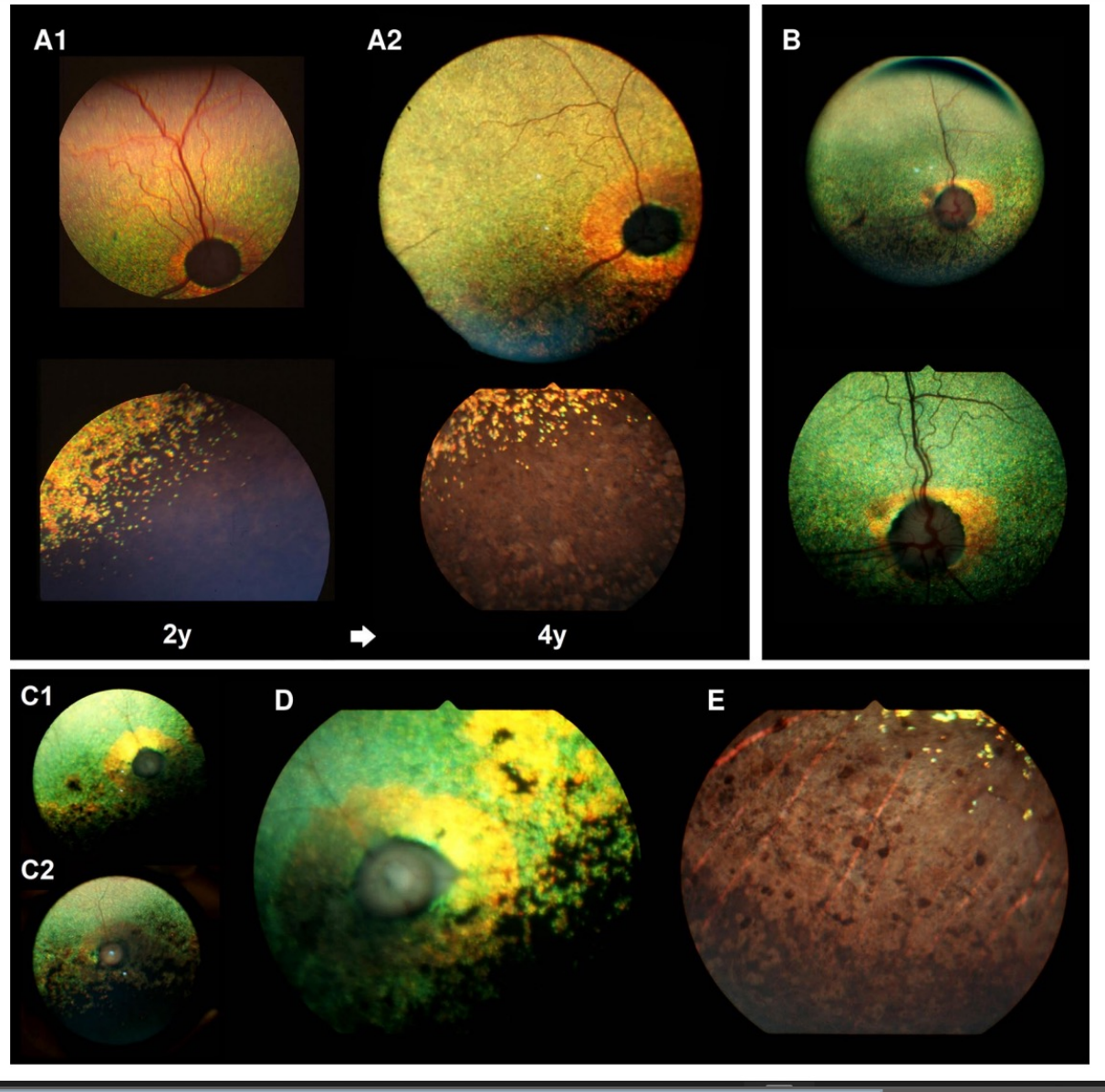
Conclusions

We have identified a LINE-1 insertion upstream of the *IMPG2* gene that strongly segregates with PRA in LA dogs. Extensive genotyping of this variant in multiple breeds strongly suggested that the LINE-1 insertion is private to the LA and was only present in PRA-affected dogs. Utilisation of the PRA4 DNA test will, over time, help reduce the frequency and incidence of this mutation in the LA breed.

CCDC66 frameshift variant associated with a new form of early-onset progressive retinal atrophy in Portuguese Water Dogs

Leonardo Murgiano[1], Doreen Becker[1,2], Courtney Spector[1], Kendall Carlin[1], Evelyn Santana[1], Jessica K. Niggel[1], Vidhya Jagannathan[3], Tosso Leeb[3], Sue Pearce-Kelling[4], Gustavo D. Aguirre[1] & Keiko Miyadera[1]✉

Aberrant photoreceptor function or morphogenesis leads to blinding retinal degenerative diseases, the majority of which have a genetic aetiology. A variant in ***PRCD*** previously identified in Portuguese Water Dogs (PWDs) underlies prcd (progressive rod-cone degeneration), an autosomal recessive progressive retinal atrophy (PRA) with a late onset at 3–6 years of age or older. Herein, we have identified a new form of early-onset PRA (EOPRA) in the same breed. Pedigree analysis suggested an autosomal recessive inheritance. Four PWD full-siblings affected with EOPRA diagnosed at 2–3 years of age were genotyped (173,661 SNPs) along with 2 unaffected siblings, 2 unaffected parents, and 15 unrelated control PWDs. GWAS, linkage analysis and homozygosity mapping defined a 26-Mb candidate region in canine chromosome 20. Whole-genome sequencing in one affected dog and its obligatory carrier parents identified a 1 bp insertion (CFA20:g.33,717,704_33,717,705insT (CanFam3.1); c.2262_c.2263insA) in *CCDC66* predicted to cause a frameshift and truncation (p.Val747SerfsTer8). Screening of an extended PWD population confirmed perfect co-segregation of this genetic variant with the disease. Western blot analysis of COS-1 cells transfected with recombinant mutant CCDC66 expression constructs showed the mutant transcript translated into a truncated protein. Furthermore, in vitro studies suggest that the mutant CCDC66 is mislocalized to the nucleus relative to wild type CCDC66. *CCDC66* variants have been associated with inherited retinal degenerations (RDs) including canine and murine ciliopathies. As genetic variants affecting the primary cilium can cause ciliopathies in which RD may be either the sole clinical manifestation or part of a syndrome, our findings further support a role for CCDC66 in retinal function and viability, potentially through its ciliary function.



Expansion of ring type lesion peripapillary
Progression of multifocal depigmentation in non-tapetal region

Memvet
Centre de referència veterinària

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PMCID: PMC6404605
PMID: 30696701

Arginine to Glutamine Variant in Olfactomedin Like 3 (*OLFML3*) Is a Candidate for Severe Goniodysgenesis and Glaucoma in the Border Collie Dog Breed

Carys A. Pugh,[*,1,2] Lindsay L. Farrell,[*,3] Ailsa J. Carlisle,[*] Stephen J. Bush,[*†] Adam Ewing,[‡] Violeta Trejo-Reveles,[*] Oswald Matika,[*] Arne de Kloet,[§] Caitlin Walsh,[§] Stephen C. Bishop,[*,4] James G. D. Prendergast,[*] Joe Rainger,[*] Jeffrey J. Schoenebeck,[*] and Kim M. Summers[*‡,2]

Abstract

Go to:

Goniodysgenesis is a developmental abnormality of the anterior chamber of the eye. It is generally considered to be congenital in dogs (*Canis lupus familiaris*), and has been associated with glaucoma and blindness. Goniodysgenesis and early-onset glaucoma initially emerged in Border Collies in Australia in the late 1990s and have subsequently been found in this breed in Europe and the USA. The objective of the present study was to determine the genetic basis of goniodysgenesis in Border Collies. Clinical diagnosis was based on results of examinations by veterinary ophthalmologists of affected and unaffected dogs from eleven different countries. Genotyping using the Illumina high density canine single nucleotide variant genotyping chip was used to identify a candidate genetic region. There was a highly significant peak of association over chromosome 17, with a *p*-value of 2×10^{-13}. Expression profiles and evolutionary conservation of candidate genes were assessed using public databases. Whole genome sequences of three dogs with glaucoma, three severely affected by goniodysgenesis and three unaffected dogs identified a missense variant in the olfactomedin like 3 (*OLFML3*) gene in all six affected animals. This was homozygous for the risk allele in all nine cases with glaucoma and 12 of 14 other severely affected animals. Of 67 reportedly unaffected animals, only one was homozygous for this variant (offspring of parents both with goniodysgenesis who were also homozygous for the variant). Analysis of pedigree information was consistent with an autosomal recessive mode of inheritance for severe goniodysgenesis (potentially leading to glaucoma) in this breed. The identification of a candidate genetic region and putative causative variant will aid breeders to reduce the frequency of goniodysgenesis and the risk of glaucoma in the Border Collie population.

Table 2

Genotype frequencies for *OLFML3* mutation c.590G>A in severely affected and unaffected dogs

Genotype for *OLFML3*	AA	AG	GG	TOTAL
Clinical status				
GWAS dogs[1]				
Glaucoma	7	0	0	7
Severe goniodysgenesis	9	1	0	10
Unaffected	1	19	22	42
Replication dogs				
Glaucoma	2	0	0	2
Severe goniodysgenesis	3	1	0	4
Unaffected	0	17	8	25
TOTALS				
Glaucoma	9	0	0	9
Severe goniodysgenesis	12	2	0	14
Unaffected	1	36	30	67

Open in a separate window

[1]Dogs that were included in the genome wide analysis (GWAS dogs) are shown separately from dogs in the replication set that were only tested for *OLFML3*.

PLoS One. 2015; 10(10): e0140436.
Published online 2015 Oct 16. doi: 10.1371/journal.pone.0140436
PMCID: PMC4608710
PMID: 26474315

Two Independent Mutations in *ADAMTS17* Are Associated with Primary Open Angle Glaucoma in the Basset Hound and Basset Fauve de Bretagne Breeds of Dog

James A. C. Oliver,* Oliver P. Forman, Louise Pettitt, and Cathryn S. Mellersh

Mutations in *ADAMTS10* (CFA20) have previously been associated with primary open angle glaucoma (POAG) in the Beagle and Norwegian Elkhound. The closely related gene, *ADAMTS17*, has also been associated with several different ocular phenotypes in multiple breeds of dog, including primary lens luxation and POAG. We investigated *ADAMTS17* as a candidate gene for POAG in the Basset Hound and Basset Fauve de Bretagne dog breeds.

Comparative Study > Invest Ophthalmol Vis Sci. 2013 Mar 13;54(3):1881-6. doi: 10.1167/iovs.12-10796.

Screening ADAMTS10 in dog populations supports Gly661Arg as the glaucoma-causing variant in beagles

John Kuchtey [1], Jessica Kunkel, Douglas Esson, John S Sapienza, Daniel A Ward, Caryn E Plummer, Kirk N Gelatt, Rachel W Kuchtey

> G3 (Bethesda). 2023 Aug 30;13(9):jkad152. doi: 10.1093/g3journal/jkad152.

Identification of an ADAMTS2 frameshift variant in a cat family with Ehlers-Danlos syndrome

Rebecca Simon [1], Sarah Kiener [2 3], Nina Thom [4], Laura Schäfer [4], Janina Müller [5], Elfi K Schlohsarczyk [5], Ulrich Gärtner [6], Christiane Herden [5], Tosso Leeb [2 3], Gesine Lühken [1]

> PLoS One. 2013 Sep 11;8(9):e74372. doi: 10.1371/journal.pone.0074372. eCollection 2013.

Dogs and humans share a common susceptibility gene SRBD1 for glaucoma risk

Nobuyuki Kanemaki [1], Kissaou T Tchedre, Masaki Imayasu, Shinpei Kawarai, Masahiro Sakaguchi, Atsushi Yoshino, Norihiko Itoh, Akira Meguro, Nobuhisa Mizuki

> Am J Vet Res. 2018 Jan;79(1):98-106. doi: 10.2460/ajvr.79.1.98.

Evaluation of ADAMTS17 in Chinese Shar-Pei with primary open-angle glaucoma, primary lens luxation, or both

James A C Oliver, Sophie Rustidge, Louise Pettitt, Christopher A Jenkins, Fabiana H G Farias, Elizabeth A Giuliano, Cathryn S Mellersh

> Anim Genet. 2019 Oct;50(5):543-545. doi: 10.1111/age.12825. Epub 2019 Jul 11.

A homozygous ADAMTS2 nonsense mutation in a Doberman Pinscher dog with Ehlers Danlos syndrome and extreme skin fragility

J A Jaffey [1], G Bullock [2], E Teplin [3], J Guo [2], N A Villani [2], T Mhlanga-Mutangadura [2], R D Schnabel [4], L A Cohn [5], G S Johnson [2]

Gene	Disease	Breed
ADAMTS 2	Dermatosparaxis Ehlers Danlos Syndrome	Pinscher Cat
ADAMTS 10	POAG	Beagle Norwegian Elkhound
ADAMTS 17	POAG Lens lux	Many breeds Terriers Basset Hound Norwegian Elkhound Fauve Bretagne Shar-pei
OLFML3	Goniodysgenesis Glaucoma	Border Collie
SRBD1	Glaucoma	Shiba-Inu / Shih-Tzu

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PMCID: PMC6171790
PMID: 30286082

Direct-to-consumer DNA testing of 6,000 dogs reveals 98.6-kb duplication associated with blue eyes and heterochromia in Siberian Huskies

Petra E. Deane-Coe, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing,[1] Erin T. Chu, Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing,[1] Andrea Slavney, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing,[1] Adam R. Boyko, Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing,[1,2,‡*] and Aaron J. Sams, Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing – review & editing[1,‡*]

Abstract

Go to:

Consumer genomics enables genetic discovery on an unprecedented scale by linking very large databases of personal genomic data with phenotype information voluntarily submitted via web-based surveys. These databases are having a transformative effect on human genomics research, yielding insights on increasingly complex traits, behaviors, and disease by including many thousands of individuals in genome-wide association studies (GWAS). The promise of consumer genomic data is not limited to human research, however. Genomic tools for dogs are readily available, with hundreds of causal Mendelian variants already characterized, because selection and breeding have led to dramatic phenotypic diversity underlain by a simple genetic structure. Here, we report the results of the first consumer genomics study ever conducted in a non-human model: a GWAS of blue eyes based on more than 3,000 customer dogs with validation panels including nearly 3,000 more, the largest canine GWAS to date. We discovered a novel association with blue eyes on chromosome 18 ($P = 1.3x10^{-68}$) and used both sequence coverage and microarray probe intensity data to identify the putative causal variant: a 98.6-kb duplication directly upstream of the Homeobox gene *ALX4*, which plays an important role in mammalian eye development. This duplication is largely restricted to Siberian Huskies, is strongly associated with the blue-eyed phenotype (chi-square $P = 5.2x10^{-290}$), and is highly, but not completely, penetrant. These results underscore the power of consumer-data-driven discovery in non-human species, especially dogs, where there is intense owner interest in the personal genomic information of their pets, a high level of engagement with web-based surveys, and an underlying genetic architecture ideal for mapping studies.

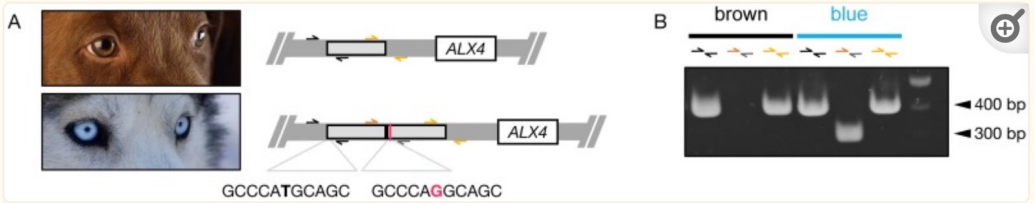


Fig 2

PCR genotyping of a tandem duplication upstream of *ALX4* associated with blue eye color.

A)* Schematic view of brown- and blue-eyed alleles (not to scale). The duplication sits head to tail to the ancestral sequence. Three sets of primers were used to amplify three regions (primers denoted with single headed arrows). Sanger sequencing of the duplication midpoint show nearly perfect synteny to canFam3.1 chr18:44791409–44791553 and 44890066–44890185. A single basepair difference, highlighted in red, show a T in the duplication sequence that corresponds to a G at chr18:44791413 in the ancestral sequence. B) PCR genotyping of one brown-eyed and one blue-eyed dog. Primer pairs denoted above each PCR lane. The 5' and 3' flanking regions amplify in both the brown- and blue-eyed alleles; the duplication midpoint amplifies only in the blue-eyed allele.

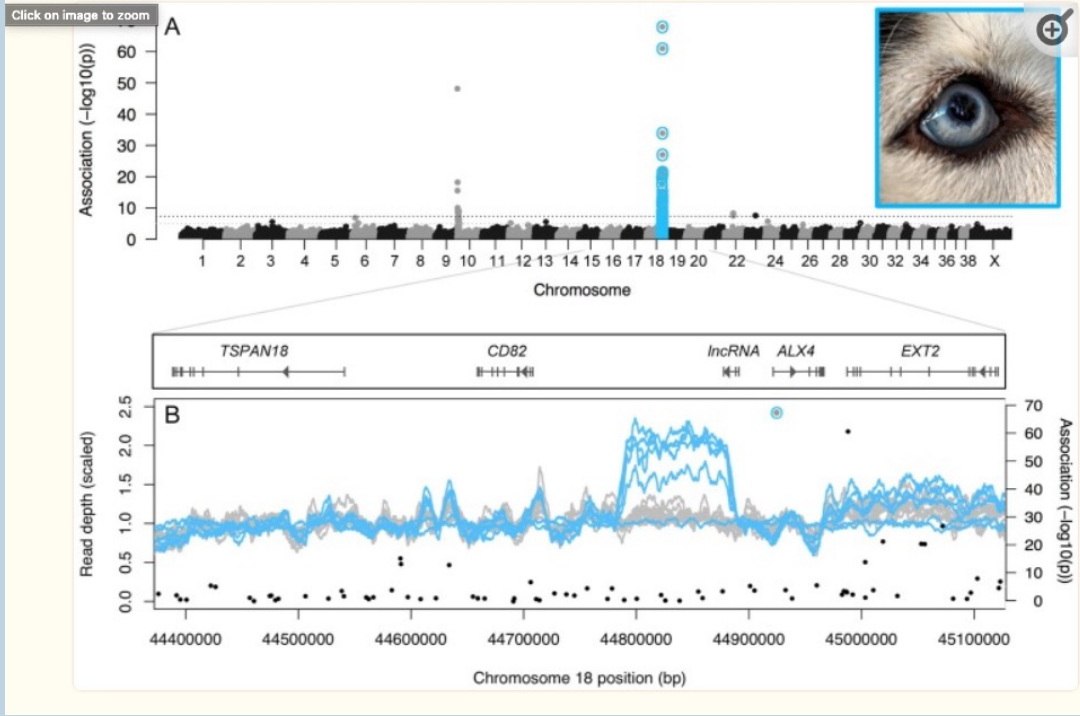
The novel association on CFA18, located in the first intron of *ALX4*, was robust to whether heterochromia (complete or sectoral) was considered (solid blue only $P = 3x10^{-71}$, heterochromia only $P = 1x10^{-12}$; S2 Fig), and remained strong when we restricted our analysis to only purebred or mixed-breed dogs (purebred $P = 3x10^{-9}$, mixed-breed $P = 3x10^{-63}$; S3 Fig). Although the minor allele (A) at the CFA18 locus was carried (in one or two copies) by only 10% of dogs in this dataset (both blue- and brown-eyed), it was carried by 78% of non-merle blue-eyed dogs (32% homozygous, 68% heterozygous) and 100% of blue-eyed purebred Siberian Huskies ($N = 22$).

- Using genetic information from people's pets (6000 dogs)
  - can help discover important genetic traits and diseases
- Researchers use large databases with genetic and physical information from pets
- Large-scale genetic studies emphasize the power of using consumer genetics for studying pets
- People's interest in their pets' genetics can help advance research

PLoS Genet. 2018 Oct; 14(10): e1007648. PMCID: PMC6171790
Published online 2018 Oct 4. doi: 10.1371/journal.pgen.1007648 PMID: 30286082

Direct-to-consumer DNA testing of 6,000 dogs reveals 98.6-kb duplication associated with blue eyes and heterochromia in Siberian Huskies

Petra E. Deane-Coe, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing,[1] Erin T. Chu, Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing,[1] Andrea Slavney, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing,[1] Adam R. Boyko, Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing,[1,2,‡*] and Aaron J. Sams, Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing – review & editing[1,‡*]



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PMID: 25969983

Impact of Facial Conformation on Canine Health: Corneal Ulceration

Rowena M. A. Packer,[1,*] Anke Hendricks,[1] and Charlotte C. Burn[2]

Carlos Eduardo Ambrósio, Academic Editor

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Abstract

Go to:

Concern has arisen in recent years that selection for extreme facial morphology in the domestic dog may be leading to an increased frequency of eye disorders. Corneal ulcers are a common and painful eye problem in domestic dogs that can lead to scarring and/or perforation of the cornea, potentially causing blindness. Exaggerated juvenile-like craniofacial conformations and wide eyes have been suspected as risk factors for corneal ulceration. This study aimed to quantify the relationship between corneal ulceration risk and conformational factors including relative eyelid aperture width, brachycephalic (short-muzzled) skull shape, the presence of a nasal fold (wrinkle), and exposed eye-white. A 14 month cross-sectional study of dogs entering a large UK based small animal referral hospital for both corneal ulcers and unrelated disorders was carried out. Dogs were classed as affected if they were diagnosed with a corneal ulcer using fluorescein dye while at the hospital (whether referred for this disorder or not), or if a previous diagnosis of corneal ulcer(s) was documented in the dogs' histories. Of 700 dogs recruited, measured and clinically examined, 31 were affected by corneal ulcers. Most cases were male (71%), small breed dogs (mean± SE weight: 11.4±1.1 kg), with the most commonly diagnosed breed being the Pug. Dogs with nasal folds were nearly five times more likely to be affected by corneal ulcers than those without, and brachycephalic dogs (craniofacial ratio <0.5) were twenty times more likely to be affected than non-brachycephalic dogs. A 10% increase in relative eyelid aperture width more than tripled the ulcer risk. Exposed eye-white was associated with a nearly three times increased risk. The results demonstrate that artificially selecting for these facial characteristics greatly heightens the risk of corneal ulcers, and such selection should thus be discouraged to improve canine welfare.

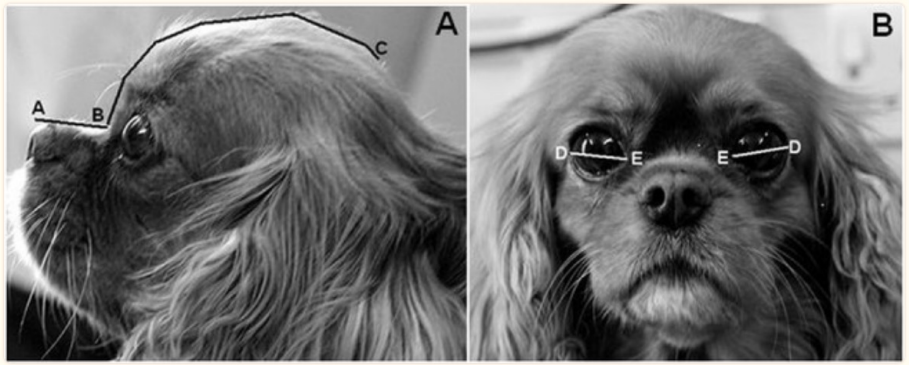

Fig 2

Quantifying muzzle length (A-B), cranial length (B-C) and palpebral fissure width (D-E).

A, left: Muzzle length is defined as the distance (mm) from the dorsal tip of the nasal planum to the stop. Cranial length is defined as the distance (mm) from the stop to the occipital protruberance. **B, right:** Palpebral fissure width is defined as the straight-line distance (mm) between the medial and lateral canthus. As an example, this Cavalier King Charles Spaniel has a craniofacial ratio of 0.27 (muzzle length 28mm / cranial length 102mm), and a relative palpebral fissure width value of 33.3% ((palpebral fissure width 34mm / cranial length 102mm) *100)

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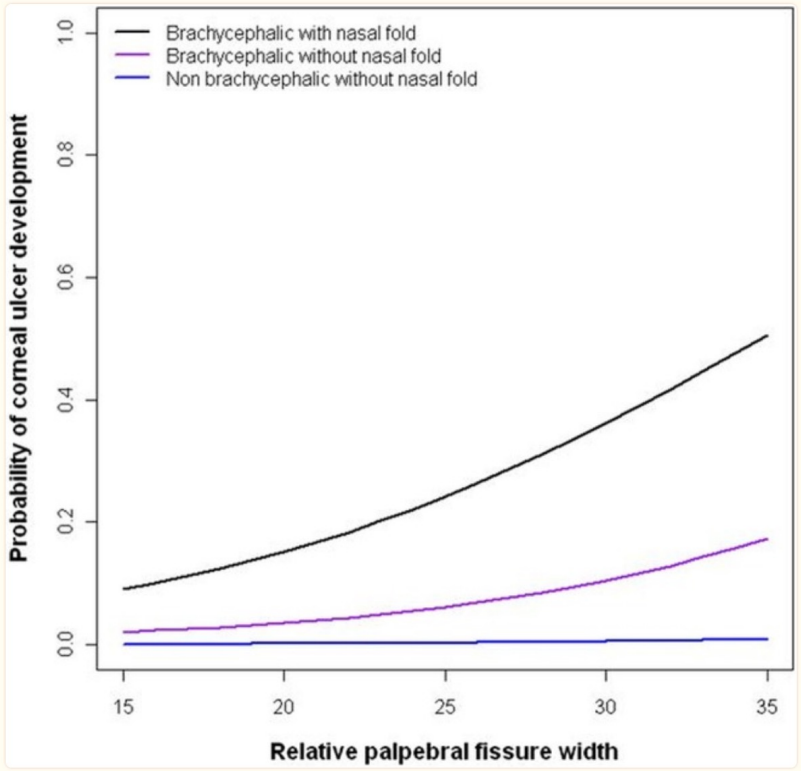
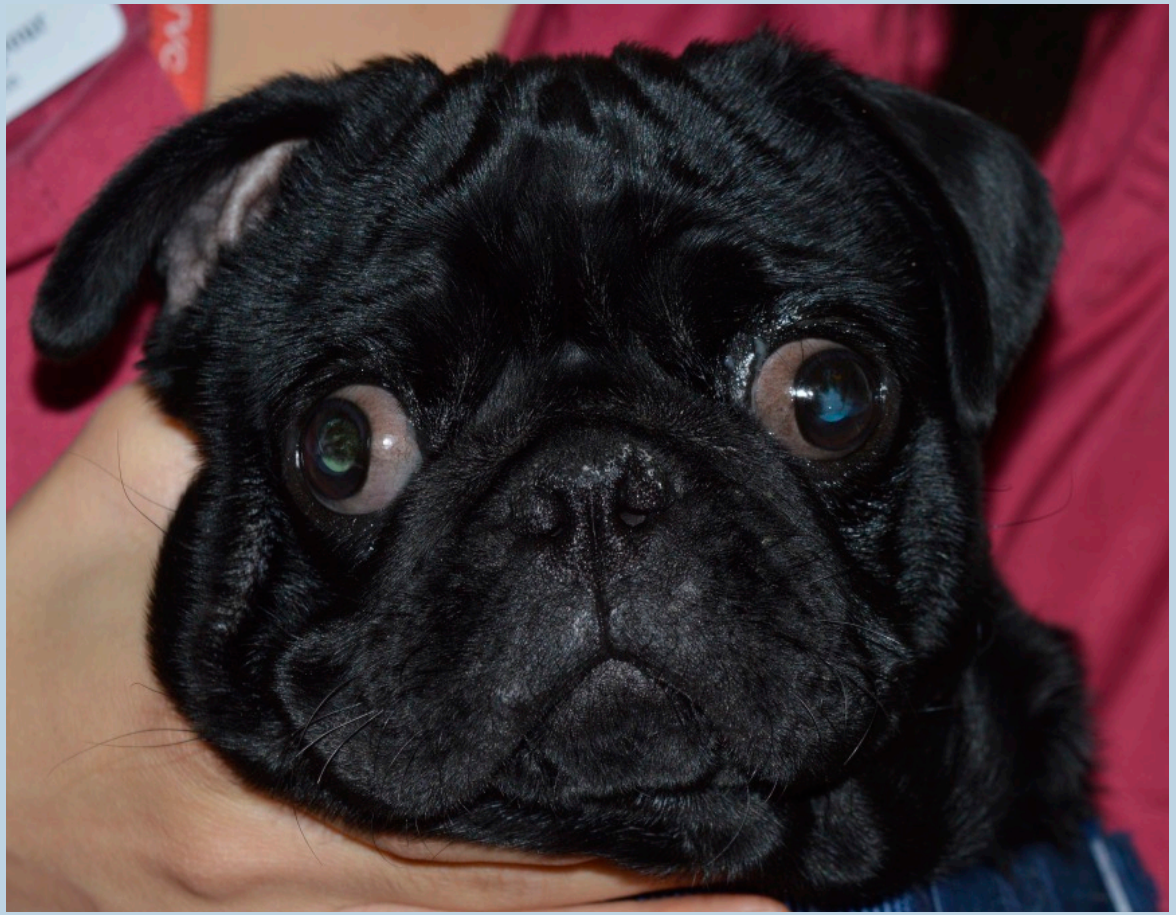
Impact of Facial Conformation on Canine Health: Corneal Ulceration

Rowena M. A. Packer, [1,*] Anke Hendricks, [1] and Charlotte C. Burn [2]

Carlos Eduardo Ambrósio, Academic Editor





Benefits of medial canthoplasty?

- 271 brachycephalic dogs
  - 43.5 underwent surgery
- **Post-operative complications:** 5.7% (6/104) had corneal ulceration post-operatively
- 271 brachycephalic dogs recommended for Medial Canthoplasty (MC)
  - 43.5% (118/271) underwent surgery - 72.0% (85/118) were Pugs
  - 5.7% had corneal ulceration postop
- 73.7% had current or historical corneal ulceration
- **Post-operative complications:** Among 104 dogs with follow-up data:5.7% (6/104) had corneal ulceration post-operatively.
- **Satisfaction:** 89.5% were satisfied with the clinical outcome.
- 87.5% were satisfied with the cosmetic outcome.
- **Conclusion:** MC has high clinical relevance for managing brachycephalic ocular syndrome, restoring functional conformation, and improving quality of life for affected dogs

animals MDPI

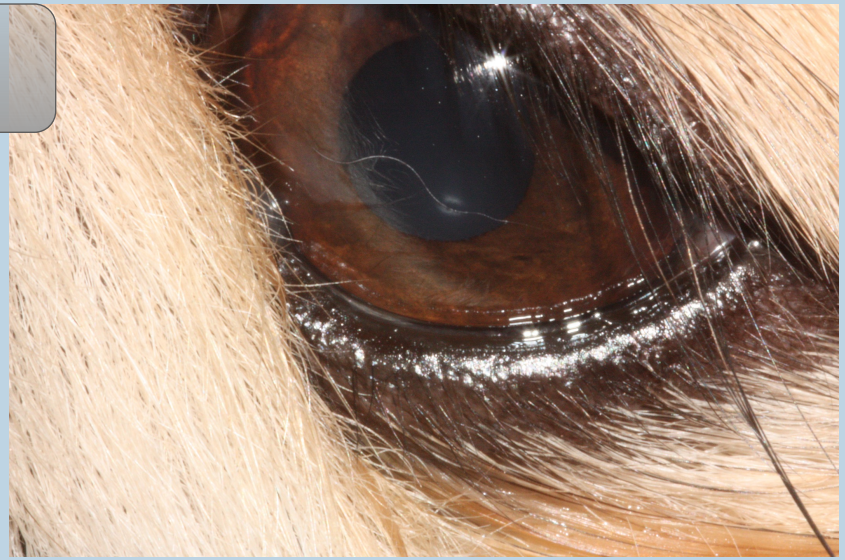
Article

A Review of Clinical Outcomes, Owner Understanding and Satisfaction following Medial Canthoplasty in Brachycephalic Dogs in a UK Referral Setting (2016–2021)

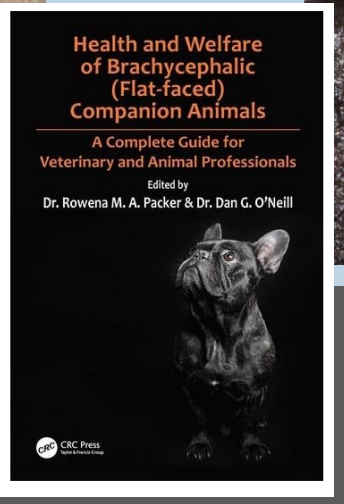
Amy L. M. M. Andrews [1,*], Katie L. Youngman [1], Rowena M. A. Packer [2], Dan G. O'Neill [3] and Christiane Kafarnik [1]

Abstract: Brachycephalic breeds have increased in popularity despite growing awareness of their predisposition to a wide range of conformation-related diseases. The extreme facial conformation of many popular brachycephalic breeds compromises their ocular surface health, increasing the risk of painful corneal ulceration. Medial canthoplasty (MC) is a surgical procedure to address ocular abnormalities in brachycephalic dogs, which are collectively referred to as brachycephalic ocular syndrome (BOS). This study retrospectively reviewed the records of dogs recommended MC at a referral hospital between 2016 and 2021. A questionnaire was designed to identify owners' perceptions pre- and post-operatively. From 271 brachycephalic dogs recommended MC, 43.5% (118/271) underwent surgery and 72.0% (85/118) were Pugs. The majority of dogs (73.7%, 87/118) that underwent surgery had current or historical corneal ulceration. Follow-up was available in 104 dogs, of which 5.7% (6/104) had corneal ulceration post-operatively. Sixty-four owners completed the questionnaire and reported post-operative corneal ulceration in 12.5% of dogs (8/64), reduced ocular discharge (70.8%, 34/48), reduced ocular irritation (67.7%, 21/31) and less periocular cleaning (52.5%, 32/61). Owners were satisfied with the clinical (85.9%, 55/64) and cosmetic (87.5%, 56/64) outcome. In conclusion, MC has high clinical relevance for the surgical management of BOS, restoring functional conformation and improving the quality of life of affected dogs.

Presentation



6 weeks post nasal fold resection



REVIEW

Exceptional Changes in Skeletal Anatomy under Domestication: The Case of Brachycephaly

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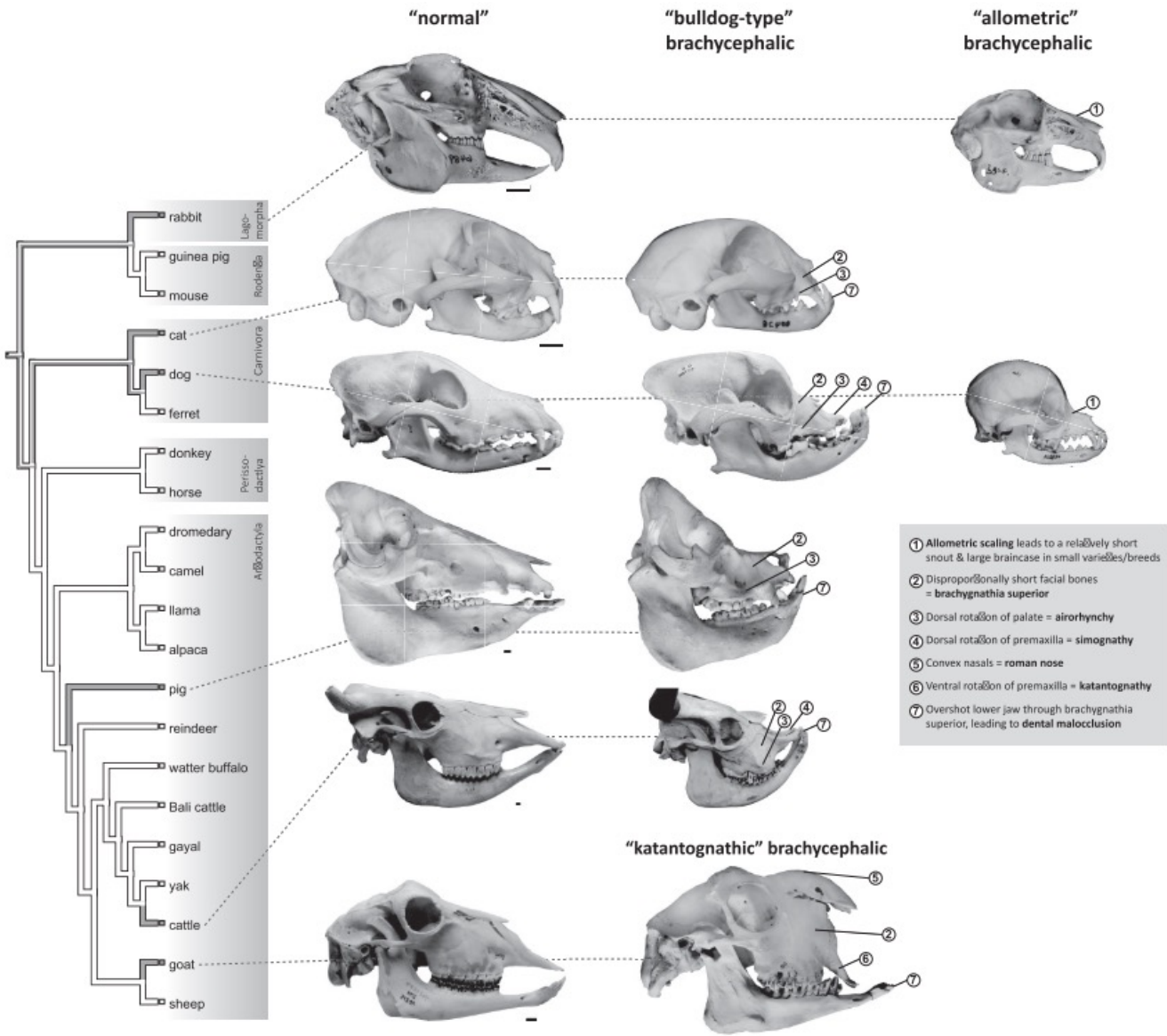


Fig. 1 Summary of brachycephalic varieties in domestic mammal species. Cladogram (branches contain no information on divergence times) shows ancient mammal domesticates (domesticated >500 YBP, see text; tree topology is according to Meredith et al. 2011 and Agnarsson and May-Collado 2008). Gray branches indicate species with at least one variety/breed where a brachycephalic phenotype is considered to occur relatively consistently or is breed defining and not just occurring occasionally, e.g., as a pathology (see text and Table 2). Skulls categorized as "normal" (left column) represent the non-brachycephalic condition in the respective domesticates. Skulls in the other columns represent brachycephalic varieties/breeds, according to the groupings as described in the text ("bulldog type," "katantognathic," and "allometric"). Numbers indicate discussed characteristics of the brachycephalic phenotype. It is evident that not all domestic species are represented by brachycephalic varieties and that the phenotype that is usually termed "brachycephalic" is variable in the different species. From left to right and top to bottom: Angora rabbit (Zoologisches Institut/Populationsgenetik [former Institut für Haustierkunde], Christian-Albrechts-Universität zu Kiel, Germany; I.f.H. 6489, mirrored); Polish rabbit ("Hermelinkaninchen," I.f.H. 5348); domestic cat of unknown breed (I.f.H. 12689); Persian cat (I.f.H. 20428, mirrored); domestic dog of unknown breed (Paleontological Institute and Museum, University of Zurich; PIMUZ A/V 608); Boxer (PIMUZ A/V 2836, mirrored); Chihuahua (Albert Heim collection at the Naturhistorisches Museum Bern, Switzerland; NMBE 1052001); domestic pig of unknown breed (Zoological Museum, University of Zurich; ZMZH 17676); brachycephalic domestic pig of unknown breed (Nehring-Collection [Zoologische Sammlung der Königlichen Landwirtschaftlichen Hochschule zu Berlin] at the Museum für Naturkunde Berlin, Germany; ZMB_Mam_106884); domestic cattle of unknown breed (PIMUZ A/V 2, mirrored); Niata cattle (Natural History Museum of Denmark; NHMD-ZMK-MK-1109, mirrored; courtesy Kristian Murphy Gregersen); mixed breed goat (Center of Natural History, University of Hamburg; ZMH 10895, mirrored); and "Egyptian goat" ("Ägyptische Ziege"; Naturmuseum Wien, Austria; NMW 2074). "Normal" skulls are scaled to the same length across species and brachycephalic skulls are scaled to the non-brachycephalic ones of the same species; scale bars equal 1 cm. Specimens are dentally mature, except the brachycephalic pig. Cattles are shown with (graphically) cut horns. Erratum concerning figure 1e in Veitschegger et al. (2018): the schematic depiction of a brachycephalic cat skull (modified from Schlueter et al. 2009) shows a Persian cat, not a Siamese cat.

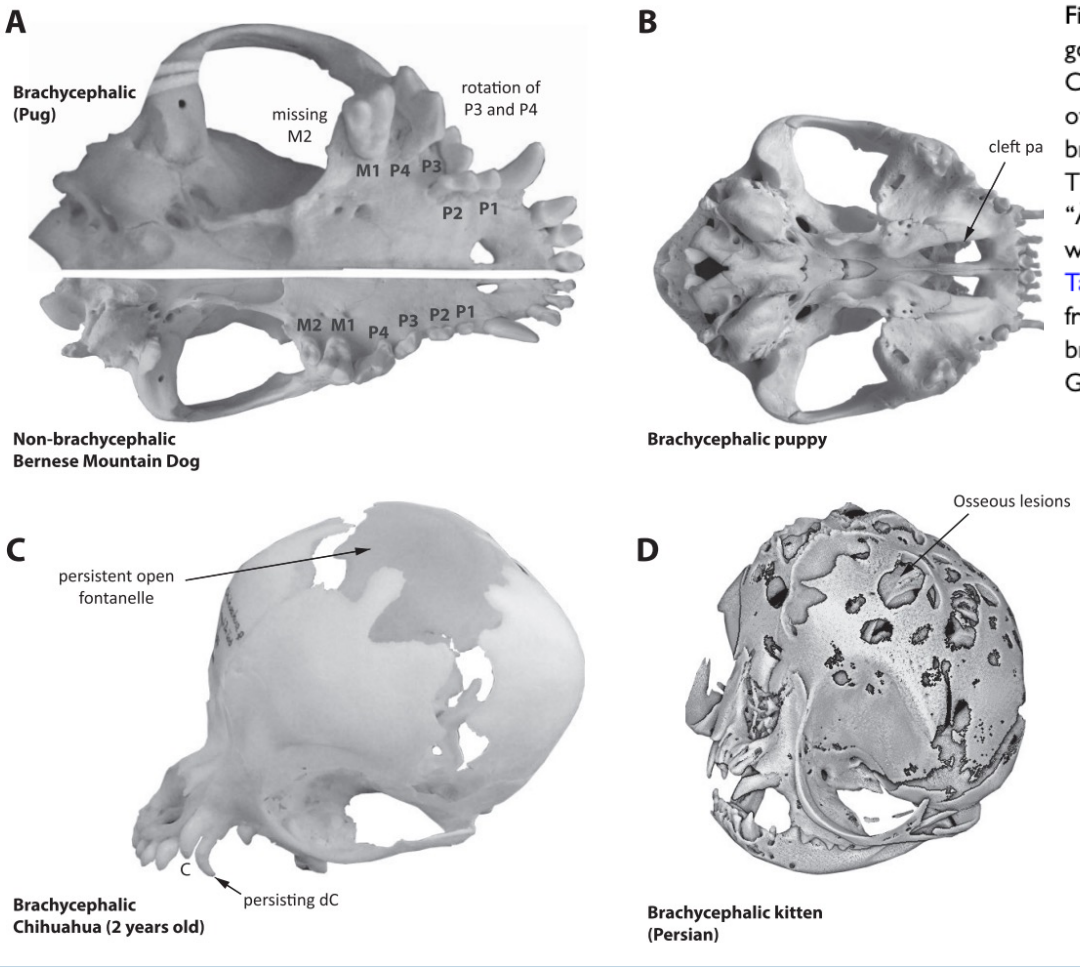
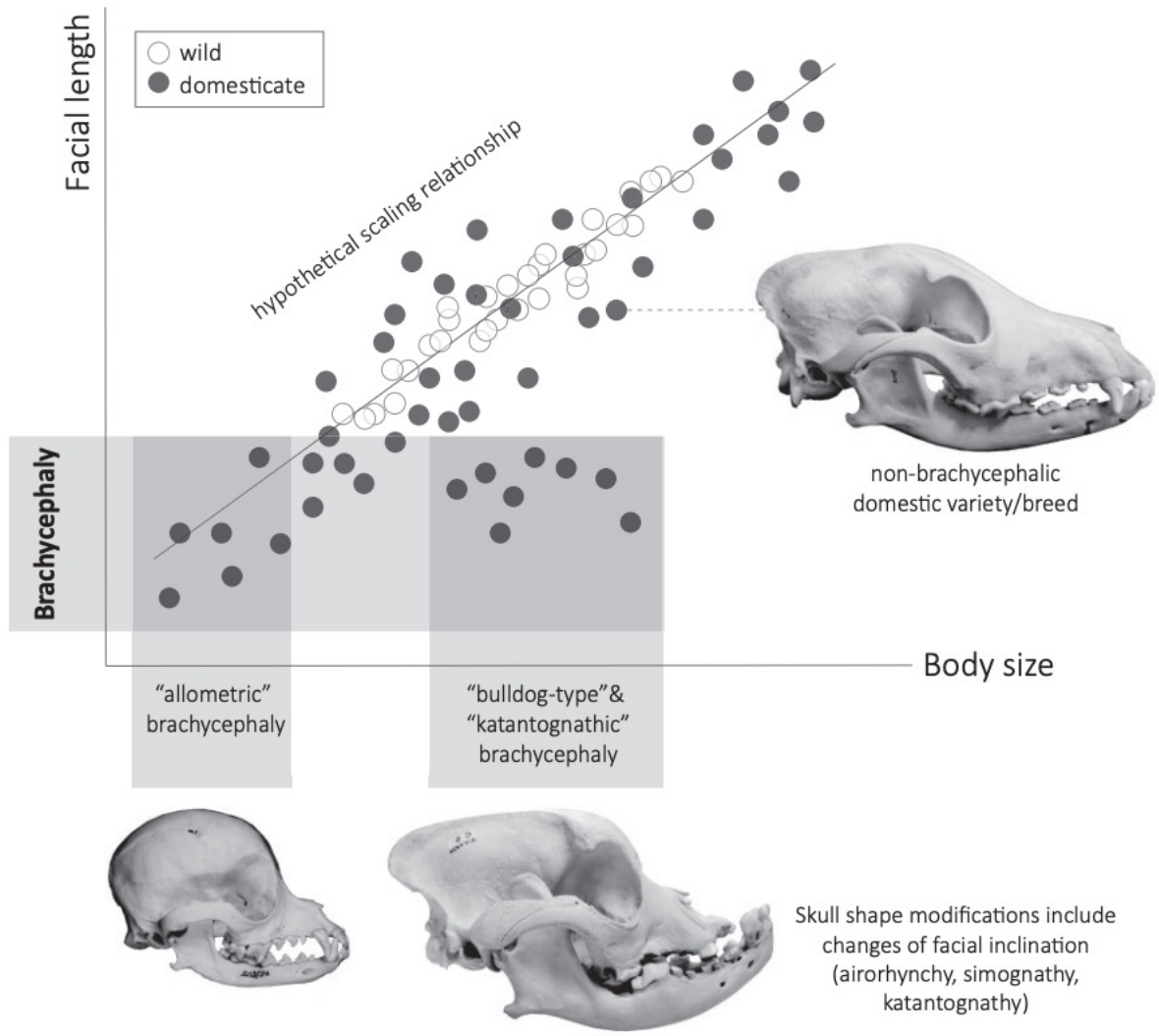


Fig. 3 Facial shape variation and brachycephaly in domestic ruminants. Certain varieties and breeds of sheep (**A**; Valais Blacknose sheep) and goats (**B**; breed unknown, Bangalore, India) exhibit a convex profile of the nose, which is termed "roman nose" (shown as a dashed line in panel C). These variations are mostly relatively mild and do not result in discordance between maxilla and mandible length, as shown on the example of the skull of a Valais Blacknose sheep (**C**; Musée de la Nature du Valais, Switzerland; HN 2010511). However, in certain goat varieties and breeds, such as Jamnapari/Etawah goats (**D**), extreme "roman nose" may be associated with an overshot lower jaw and dental malocclusion. The overshot lower jaw and dental malocclusion (dashed circles in panel E) are shown on the example of the skull of an "Egyptian goat" (**E**; "Ägyptische Ziege"; Naturmuseum Wien, Austria; NMW 2074). These varieties/breeds could be classified as "katantognathic" brachycephalic, where, in addition to the extremely convex nasal bones, parts of the snout (premaxilla) are foreshortened and downward tilted (Fig. 1 and Table 1). In other domestic ruminants, such as cattle, no cases of "katantognathic" brachycephaly are known. Instead, the extinct Niata cattle from South America (**F**, reconstruction) is characterized by shortened and upward tilted facial bones (**G**), which is indicative of "bulldog-type" brachycephaly (Fig. 1), and may also lead to dental malocclusion (G). Pictures are not to scale. Credits: A, Benjamin Jost; B, C, E: Madeleine Geiger; D, Shutterstock: Ibenk_88; F, G: Artwork by Jorge González.

Fig. 5 Examples of craniodental anomalies that may cooccur with "bulldog-type" and "allometric" brachycephaly. **(A)** An example of a brachycephalic pug (left ventral aspect of cranium; Naturhistorisches Museum Bern, collection of the Albert Heim Foundation, Switzerland; NMBE 1062021) showing crowding of the postcanine teeth and a rotation of the third and fourth upper premolars (P3 and P4) relative to the longitudinal axis of the cranium. Additionally, the second upper molar (M2) is missing (note that there is little space caudal to M1 to house such a tooth). As a comparison, the example of a non-brachycephalic Bernese Mountain Dog (right ventral aspect of skull; NMBE 1050197) below shows the wild-type dental formula and much less to absent dental crowding and rotation. **(B)** An example of a cleft palate (bony portion) in the cranium of a puppy of a bulldog (photo by R.A.S. of specimen from his personal collection). **(C)** An example of a 2-year-old Chihuahua (NMBE 1051992) exhibiting persistent open fontanelles and a deciduous canine tooth (dC), next to the permanent canine (C). Usually in dogs, the fontanelle fuses a few days or weeks after birth (De Lahunta and Glass 2009) and the deciduous canines are usually replaced by about a half a year of age (Habermehl 1975). (**D**) Osseous defects in the parietal and frontal bones of a 5-day-old Persian kitten (Schmidt et al. 2017). Skulls are not to scale. Please note that this list of characteristics is not exhaustive. For more craniodental anomalies associated with brachycephaly, also including soft tissue, see text.



Allometric brachycephaly refers to skull shape variation where the facial length shortens relative to the braincase, predominantly due to smaller body size rather than other anatomical changes.

The shortening of the snout is proportional to the animal's overall body size and results from natural scaling relationships between the size of different parts of the skull and body

Fig. 4 Hypothetical scaling relationship between body size and facial length in any wild animal (white dots) and its domestic counterpart (black dots). The latter exhibit larger intragroup variation of body size and facial length, visualized via more scattering of dots along the common scaling axis (straight line). This comparison exemplifies the difference between "short snoutedness," i.e., brachycephaly (black dots incorporated into the horizontal box), due to small size ("allometric" brachycephaly) and due to shortening of facial bones not directly resulting from small body size ("bulldog-type" brachycephaly or "katantognathic" brachycephaly). The latter is usually associated with skull modifications, including changes of facial inclination, whereas the former is not per se. Brachycephalic skull proportions may not occur in the respective wild forms. Photographs of skulls depict domestic dogs as an example (for details on specimens, see Fig. 1). The skulls are to scale.

Egiptian horses

News > UK News

NEIGH LAUGHING MATTER Vets slam ‘cartoon horses’ being bred with concave faces to look like Disney animals

Outrage from experts comes following the birth of thoroughbred colt El Rey Magnum, which is said to be at risk of breathing problems because of its unnatural shape

Brief

- Reviewed recent genetic diseases in dogs
- Did I forget about cats??
  - Absolutely not, I did not find new articles! ☹
- Discussed benefits of medial canthoplasty
- Discussed brachycephaly