

Article

Congenital ocular anomalies in purebred and crossbred Rocky and Kentucky Mountain horses in Canada

Bruce H. Grahn, Chantale Pinard, Sheila Archer, Rebecca Bellone, George Forsyth, Lynne S. Sandmeyer

Abstract – Multiple congenital ocular anomalies in purebred and crossbred Rocky and Kentucky Mountain horses in Canada are frequently diagnosed with biomicroscopic and indirect ophthalmoscopic examination. In order of frequency detected, these include temporal ciliary epithelial cysts; iridal hypoplasia; prominent corneas; focal temporal retinal degeneration related to ciliary cysts; and, rarely, retinal detachment. A pedigree analysis confirms a dominant mode of inheritance with incomplete penetrance and with a linkage to coat color.

Résumé – **Anomalie oculaires congénitales chez des chevaux Rocky et Kentucky Mountain de race pure et croisée au Canada.** Des anomalies oculaires congénitales multiples chez des chevaux Rocky et Kentucky Mountain de race pure et croisée au Canada sont souvent diagnostiquées par examens biomicroscopiques et ophtalmoscopiques indirects. Par ordre de fréquence, les anomalies détectées comprennent les kystes épithéliaux ciliaires temporaires, l'hypoplasie iridienne, la cornée proéminente, la dégénération focale de la rétine temporale reliée aux kystes ciliaires et, rarement, le détachement de la rétine. Une analyse du pedigree confirme un mode dominant de transmission génétique avec pénétrance incomplète et liaison à la couleur de la robe.

(Traduit par Docteur André Blouin)

Can Vet J 2008;49:675–681

Introduction

Inherited congenital multiple ocular anomalies in Rocky Mountain horses were originally reported by Ramsey et al (1). There are 2 phenotypes of ocular manifestation of these anomalies: temporal ciliary cysts and temporal ciliary cysts with other anomalies, including iridal hypoplasia, megalocornea, retinal dysplasia, focal cataracts, and megaloblepharon (1). The ocular anomalies reported in order of frequency detected are temporal posterior iris, ciliary and retinal cysts, temporal curvilinear streaks of retinal pigment epithelial pigmentation and proliferation, retinal dysplasia, iridal hypoplasia, megalocornea, megaloblepharon, pectinate ligament hypoplasia, and focal goniosynechia with absence of angle structures (1). Although the corneal shape appears abnormal and gives the perception of

megalocornea and anterior megalophthalmos, both may have been misinterpreted initially (1). A follow-up study by the same authors reported that there was not a significant difference in corneal size; intraocular pressures; or the thickness of the dorsal, ventral, or medial peripheral parts of the cornea of affected horses compared with control horses (2). Only the central and temporal parts of the cornea were significantly thicker, and these were unlikely to create the illusion of megalocornea or anterior megalophthalmos, leading to the conclusion that the corneal anomaly is corneal globosa, an abnormally shaped cornea (2).

Multiple ocular anomalies in these horses are inherited; the mode of inheritance proposed was codominance with expression of cysts in heterozygotes and multiple anterior segment anomalies in homozygotes, and incomplete penetrance was suggested (3). Autosomal codominant inheritance is defined as dominant expression of an allele with phenotypic differences noted between confirmed heterozygotes and homozygotes. However, an autosomal recessive mode of inheritance could not be excluded statistically, and examination of out-crosses that evaluated phenotypic ocular disease in heterozygotes and homozygotes was not reported (3).

Based on PubMed, CAB, and Google Scholar searches for the last decade (1997–2007), we did not identify reports of multiple congenital anomalies in Rocky and Kentucky Mountain horses in other countries. The objectives of this study were to determine the prevalence of congenital ocular anomalies in purebred and crossbred Rocky Mountain and Kentucky Mountain horses in Canada, to report the expression and types of anomalies present, and to provide a pedigree of related horses that identifies

Departments of Small Animal Clinical Sciences (Grahn, Sandmeyer) and Biomedical Sciences (Forsyth), Western College of Veterinary Medicine, 52 Campus Drive, University of Saskatchewan, Saskatoon, Saskatchewan S7N 5B4; Quill Lake, Saskatchewan (Archer); Department of Biology, University of Tampa, 401 W. Kennedy Blvd. Box 3F Tampa, Florida, USA (Bellone); Large Animal Hospital, Faculté de médecine vétérinaire, Université de Montréal, PO Box 5000, Saint-Hyacinthe, Québec J2S 7C6 (Pinnard).

Address all correspondence and reprint requests to Dr. Bruce H. Grahn; e-mail: bruce.grahn@usask.ca

This research was funded by a Dube-Ryan Equine research grant.

Table 1. Ocular anomalies noted in the Rocky Mountain and Kentucky Mountain horses in Canada

Breed	Rocky Mountain horses and (F ₁ and F ₂ crosses) n = 97	Kentucky Mountain horse n = 37
No abnormalities except (incipient cataracts) ^a	49 (14) ^a	25 (5) ^a
Temporal ciliary cysts (with incipient cataracts) ^a	41 (1) ^a	10
Multiple ocular anomalies (with incipient cataracts) ^a	7 ^a	2 (2) ^a

^a With incipient cataracts

the mode of inheritance and determines the relationship of the ocular anomalies to coat color.

Materials and methods

The eyes of purebred or crossbred Rocky Mountain horses, Kentucky Mountain horses, and unrelated breeds were examined by a veterinary ophthalmologist with a transilluminator, a biomicroscope (Osram 64222; Carl Zeiss Canada, Don Mills, Ontario), and an indirect ophthalmoscope (Heine Omega 200; Heine Instruments Canada, Kitchener, Ontario) after application of topical 1% tropicamide (Mydracyl; Sandoz Canada, Boucherville, Quebec) to dilate the pupils.

A pedigree was constructed with related horses to investigate the mode of inheritance of the multiple ocular anomalies and their relationship to coat color. Coat color was assessed by a coat color expert and photographs of all horses were archived for their examination.

Results

A total of 134 horses were included in this study, 97 purebred and F₁ and F₂ Rocky Mountain crosses, and 37 Kentucky Mountain horses: 48 and 12 horses of each of these groups, respectively, had ocular anomalies (ciliary epithelial cysts, iridal hypoplasia, and prominent corneas) (Table 1). The most common anomalies diagnosed in these horses were bilateral and, rarely, unilateral temporal ciliary epithelial cysts (Figure 1). Other less common bilateral ocular anomalies observed were temporal fundic curvilinear streaks (Figure 2), iridal hypoplasia (Figure 3), and a prominent corneal shape. Multiple anomalies and temporal ciliary epithelial cysts were noted in 7 affected Rocky Mountain horses and 2 Kentucky Mountain horses (Figure 4). All Rocky Mountain horses with iridal hypoplasia and prominent corneas had ophthalmoscopically detectable ciliary epithelial cysts. Cataracts were uncommon: they were noted in only 1 Rocky Mountain and 2 Kentucky Mountain horses affected with cysts and multiple ocular anomalies, but they were present in 14 Rocky Mountain and 5 Kentucky Mountain horses without cysts and other ocular anomalies. Focal retinal degeneration, demarcated by curvilinear streaks presumably related to peripheral ciliary epithelial and retinal cysts, focal retinal detachments, and retinal pigment epithelial hypertrophy and pigmentation were noted frequently in 22 Rocky Mountain horses affected with these anomalies (Figure 2). Retinal tears,

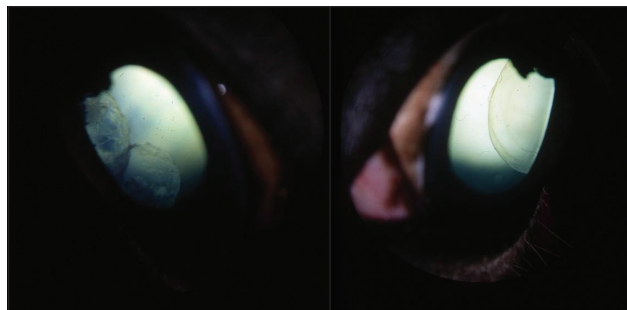


Figure 1. The most common lesions in Rocky and Kentucky Mountain horses in Canada were large temporal ciliary cysts. Most were bilateral as noted in this Rocky Mountain filly.

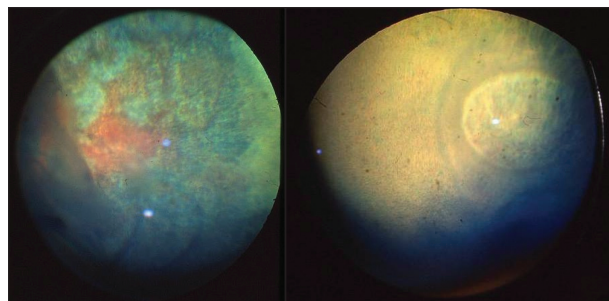


Figure 2. Other common lesions in this study were focal retinal degeneration with curvilinear streaks related to cysts and focal retinal detachment. Complete retinal detachments were uncommon. Note the hyperreflectivity in the temporal fundi of these 2 Rocky Mountain mares and the multiple curvilinear streaks.

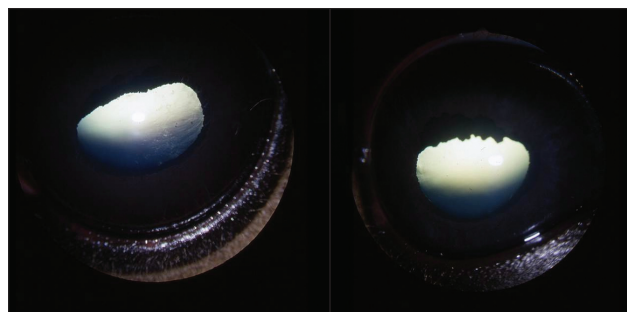


Figure 3. Iridal hypoplasia was confirmed by a lack of any substantial dilatation after 1% tropicamide was applied for approximately 30 minutes and by small pupils, encircling hypoplastic granula iridica, and thin irides.

vitreous degeneration, and rhegmatogenous retinal detachment were uncommon and noted in only 2 Rocky Mountain horses affected with ciliary cysts and multiple ocular anomalies.

The pedigree of related Rocky Mountain horses is complex and precludes sex-linked, autosomal recessive, and codominant modes of inheritance (Figure 4). Both fillies and colts in both the F₁ and the F₂ generations were affected with both phenotypes of the disease, ruling out sex-linked modes of inheritance. There were multiple F₁ foals with temporal ciliary cysts alone, and with multiple ocular anomalies and ciliary cysts born to foundation mares that were not related to Rocky or Kentucky Mountain horses (Figure 4, Table 3). This finding rules out autosomal recessive and codominant modes of inheritance. The F₂ generation sired by both foundation Rocky Mountain stallions with

Table 2. Foundation mares and stallions, breed, number, coat color, and ocular phenotype

Normal ocular examination	Incipient cataracts only	Temporal ciliary cysts only	Multiple ocular anomalies + ciliary cysts	Unknown — no ocular examination
13. Tennessee walker, chestnut	15. Kentucky × Rocky Mountain, palomino	1. Rocky Mountain, silver black	2. Rocky Mountain, silver black	0. Tennessee walker, color unknown
17. Saddlebred, chestnut	24. Saddlebred, chestnut	14. Rocky × Kentucky Mountain, silver black		3. Saddlebred, pinto tobiano
20. Tennessee walker, chestnut tobiano	25. Tennessee walker × standard bred, black	16. Rocky Mountain horse, silver black		4. Standardbred, bay
31. Tennessee walker, chestnut	26. Tennessee walker, black			5. Morgan, black
35. Arabian, grey				6. Tennessee walker, chestnut sabino
36. Saddlebred, palomino				7. Tennessee walker, chestnut sabino
37. Standardbred, chestnut				8. Saddlebred, palomino
39. Morgan, chestnut				9. Pony, palomino
40. Standardbred, bay				10. Welsh pony, bay
				12. Tennessee walker, bay
				18. Tennessee walker, black
				19. Standardbred, bay
				22. Tennessee walker, black
				23. Tennessee walker, bay
				27. Morgan, chestnut
				28. Saddlebred, palomino
				30. Saddlebred, chestnut
				32. Standardbred, bay
				34. Tennessee walker, chestnut sabino

temporal ciliary cysts (horse #1) and cysts with multiple ocular anomalies (horse #2) produced foals with no abnormalities, ciliary cysts, or ciliary cysts and multiple anomalies (Figure 4, Table 4). This finding also rules out a codominant mode of inheritance. This pedigree confirms incomplete penetrance of a dominant inherited trait. It appears that ciliary cysts and multiple ocular anomalies are expressed together or not at all in the F₁ and F₂ generations, and from repeated breedings of the same stallions and mares.

Coat color does appear to be linked to the expression of the ocular anomalies. Specifically, the silver black and silver bay colors were commonly associated with these anomalies (Tables 2–4).

Discussion

The prevalence of multiple ocular anomalies in purebred and crossbred Rocky Mountain and Kentucky Mountain horses in Canada is approximately 50%, which is similar to the prevalence reported in the USA (1). The most common anomalies were temporal uveal cysts, as previously reported by Ramsey et al (1). Focal retinal degeneration and curvilinear streaks were commonly noted and were likely related to previous focal detachments and peripheral retinal cysts. Although we do not have histological confirmation of retinal pigment epithelial pigmentation and retinal degeneration, their ophthalmoscopic

appearance was very similar to those described and confirmed with light microscopy by Ramsey et al (1).

In contrast to the study by Ramsey et al (1), we did not document any retinal folds or dysplasia with indirect ophthalmoscopy in our population of horses. This may indicate that in our population of horses, the lesions were either too small to identify with the ophthalmoscope (we did not have ocular tissues for light microscopic examination) or this population does not manifest with retinal dysplasia. Further investigations with light microscopic examination of these anomalies in these horses are required. Similarly, we did not document any filtration angle anomalies in the horses we examined. Although the irides were hypoplastic, as documented by a lack of dilatation after application of a mydriatic and by the thin iris leaflets with small encircling granula iridica, the trabecular meshwork appeared normal on biomicroscopic examination in all horses in the visible temporal and nasal areas.

Focal anterior and posterior cortical cataracts were noted only occasionally in horses affected with ciliary cysts and uveal hypoplasia, but quite frequently in horses without any of these anomalies; thus, they are not likely inherited as part of this syndrome. We also noted more horses with apparent megaloblepharon than were recorded by Ramsey et al (1) (data not shown as eyelid fissure measurements were incomplete). Megaloblepharon may contribute to the perception of increased corneal size and

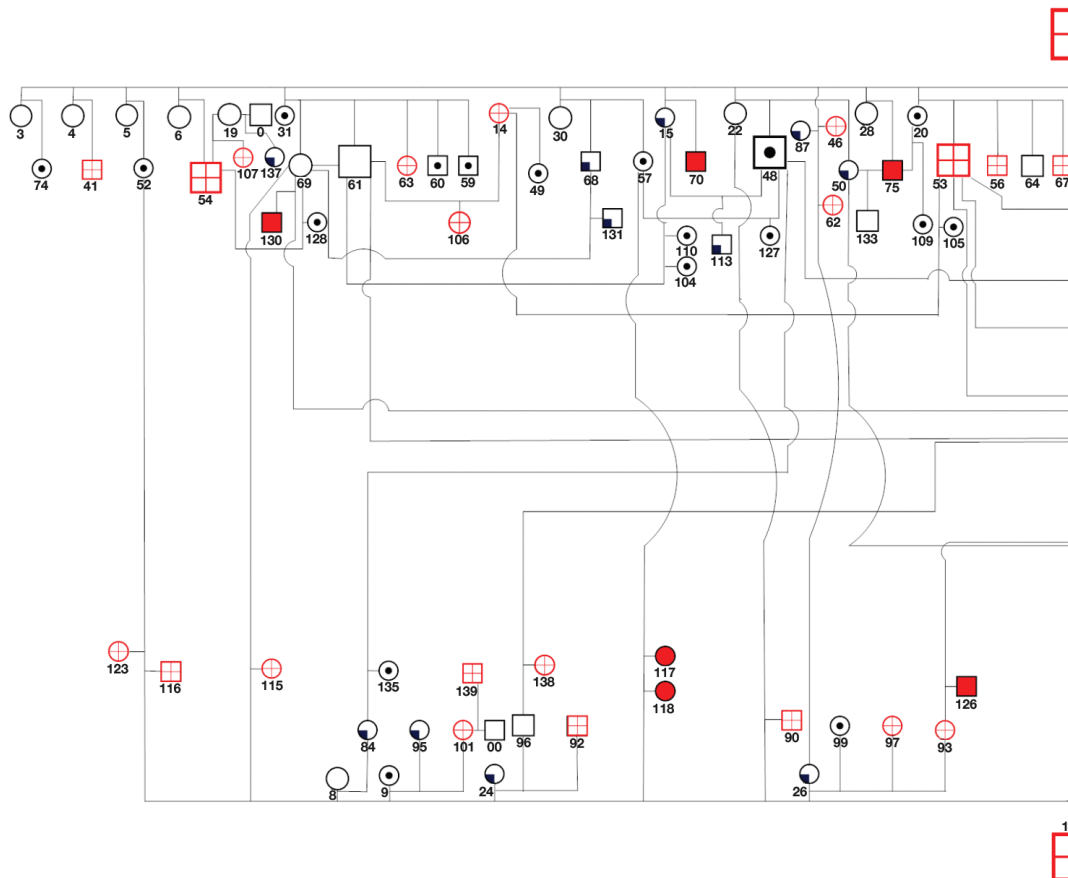


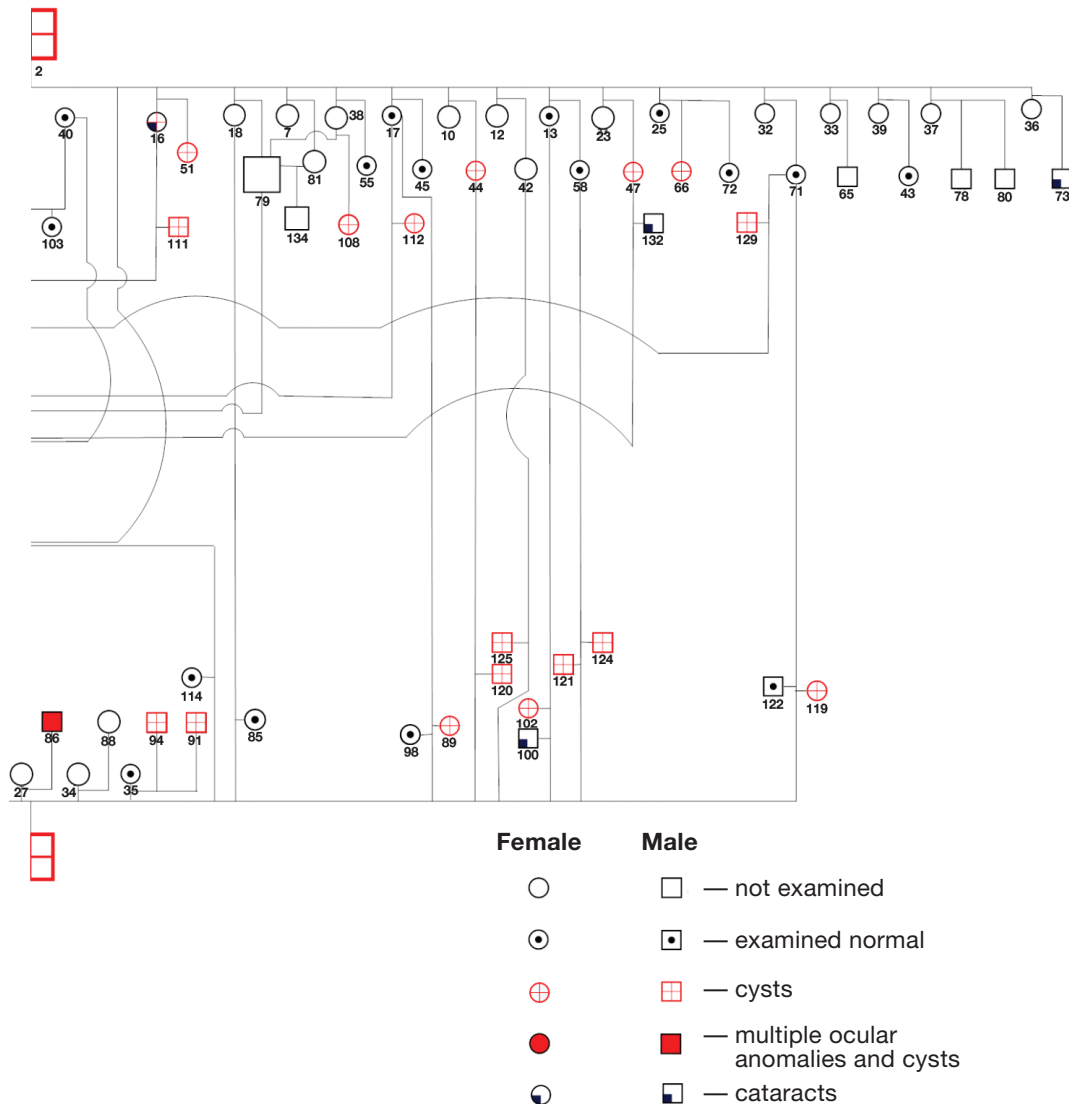
Figure 4. Pedigree of horses affected with Rocky Mountain horse eye anomaly in Canada. Note that cysts were detected in the F_1 crossbred generation sired by a Rocky Mountain stallion with cysts (all but 2 dams were gaited breeds). Note also that the F_2 generation failed to express ciliary cysts, expressed ciliary cysts alone, expressed ciliary cysts and multiple ocular anomalies, when sired by either a Rocky Mountain stallion with ciliary cysts or a Rocky Mountain stallion with ciliary cysts and multiple ocular anomalies.

scleral exposure, similar to that seen in brachycephalic dogs with euryblepharon and shallow orbits (4). Further evaluations with caliper and ultrasonographic measurements and advanced imaging (computed tomography, etc.) of the eyelid fissure and orbital structures of affected and normal horses are warranted.

We noted multiple coat colors in the horses affected with ciliary cysts and multiple ocular anomalies (Tables 2–4). In common with observations in previous studies, horses that appear to carry the silver dapple mutation (silver black and silver bay) are those that express most, but not all, of the uveal cysts and multiple ocular anomalies (1–3). The silver dapple allele dilutes black eumelanin pigment and a causative mutation has been identified (5,6). Many of the horses with ocular anomalies that we studied were chestnuts (pheomelanin production only), and it is unknown if these horses also carry the silver dapple mutation. However, 1 black horse (horse #60, Table 3) not suspected to be carrying the silver dapple mutation had an apparent

increased eyelid fissure length but no other ocular anomalies and 1 silver bay horse (horse #127, Table 4) suspected to have the silver mutation had a normal ocular examination. This may indicate that these anomalies are linked to coat color; however, they are not likely due to the silver mutation.

One of the herds we examined was unique in that 2 Rocky Mountain stallions were crossbred with multiple unrelated mares of various breeds and coat colors. Only 2 of these foundation mares were Rocky Mountain horses and expressed ciliary cysts. All the other foundation mares were varied cross breeds, including saddlebreds, standardbreds, Morgans, Tennessee walkers, Welsh ponies, and Arabians — all breeds that have not been reported with temporal retinal cysts. Although not all these mares were examined during the study period, 6 were examined and no ocular anomalies were present. These factors make it very unlikely that these foundation mares would be carriers. In addition, the F_2 generation (horses #117, 118), sired by foundation



stallion (horse #1), which had only temporal ciliary cysts out of F₁ mare (horse #57), a phenotypically normal mother, had multiple ocular anomalies (Figure 4). This would not be possible if this condition was inherited as an autosomal recessive trait, unless the mare was a carrier. In contrast to Ewart's report (3), our pedigree involved crossing Rocky Mountain stallions affected with ciliary cysts or cysts and multiple anomalies with non Rocky Mountain horses. Our pedigree confirms that codominant inheritance is not present, as mare #57, though phenotypically normal, produced offspring with multiple ocular anomalies. Rather, this disorder is inherited with a dominant mode with expression of ciliary cysts, cysts plus multiple ocular anomalies, or normal phenotype, as evidenced by the breeding of F₁ mares with 2 foundation stallions (Figure 4). The expression of these anomalies inconsistently in the F₁ and F₂ generations confirms the incomplete expression of this dominant trait.

Kentucky Mountain Horse Pedigree

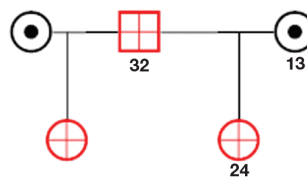


Figure 5. Pedigree of some of the Kentucky Mountain horses that were related and when examined found to be affected with uveal cysts.

Ramsey et al (1,2) and Ewart et al (3) reported that multiple ocular anomalies in the Rocky Mountain horse develop as an anterior segment dysgenesis. Inherited anterior segment dysgenesis in humans and mouse models encompasses a wide range of anomalies, including microphthalmia, Peter's anomaly,

Table 3. F₁ generation of Rocky Mountain horses with coat color and ocular phenotype

Normal ocular examination	Incipient cataracts only	Temporal ciliary cysts only	Multiple ocular anomalies + cysts	Unknown ocular examination
43. Black	50. Black	41. Silver black	51. Silver black	42. Silver black
45. Black	54. Silver black	44. Silver bay	56. Chocolate tobiano	61. Black
48. Black	57. Silver bay	46. Silver black	60. Black	65. Silver black
49. Black	58. Silver black	47. Silver black	62. Silver black	69. Silver black
52. Black tobiano	68. Bay	53. Chocolate tobiano	67. Chocolate tobiano	76. Silver black
55. Dark chestnut	73. Dark chestnut	63. Silver black	70. Silver bay	77. Silver black
59. Black	84. Chestnut	66. Silver black	75. Silver black	78. Bay
64. Black	87. Chestnut	89. Silver bay	86. Chestnut	80. Black
71. Bay	95. Palomino	93. Silver black	90. Silver black	
72. Black	137. Brown roan	97. Silver bay	91. Silver bay	
74. Black tobiano		101. Chestnut	92. Silver bay	
85. Black		102. Chestnut	94. Silver bay	
99. Chestnut		107. Chestnut	90. Chestnut	
109. Black		108. Silver bay	116. Silver bay	
110. Chestnut		111. Silver bay	126. Silver black	
113. Bay		112. Chestnut tobiano		
114. Dark Bay		115. Silver black		
122. Bay		120. Chestnut		

Table 4. F₂ generation of Rocky Mountain horses with coat color and ocular phenotype

Normal ocular examination	Incipient cataracts only	Temporal uveal cysts only	Multiple ocular anomalies + cysts	Unknown — no ocular examination
103. Dark bay	113. Bay	106. Silver black	104. Chestnut	133. Silver black
105. Chestnut tobiano	131. Chestnut	111. Silver black	108. Silver bay	134. Silver black
109. Black	132. Dark bay	112. Chestnut tobiano	116. Silver bay	
110. Chestnut		120. Chestnut	117. Dark palomino	
127. Silver bay		139. Silver bay	118. Dark palomino	
128. Red roan			119. Silver bay	
131. Chestnut			121. Chestnut	
132. Dark bay			123. Silver bay	
135. Black			124. Silver bay	
			125. Black silver mane and tail	
			138. Silver bay	

Axenfeld-Reiger syndrome, Sturge-Weber syndrome, posterior polymorphous syndrome, etc. (7–12). Anterior segment dysgenesis has been reported in animals, including aniridia in horses (13), keratolenticular dysgenesis in a kitten (14), congenital anterior staphyloma with rudimentary lens in a calf (15), and microphthalmia in dogs (16). Congenital glaucoma in the horse (17) and the llama (18) also appears to develop secondary to anterior segment dysgenesis. Congenital glaucoma is manifested with buphthalmos and microphakia, and the anterior uvea and filtration angles are always hypoplastic (17,18). The corneal endothelium plays an essential role in anterior segment development and its absence leads to anterior segment dysgenesis (19).

It is possible that Rocky Mountain horse eye anomalies develop partially as anterior segment dysgenesis, given the apparent corneal and eyelid anomalies described by Ramsey et al (1)

and Cook (20). However, the lack of inner corneal and lenticular anomalies is considered very unusual in anterior segment dysgenesis. In addition, in subsequent studies, Ramsey et al (2) have confirmed a lack of corneal enlargement and thickness. We also did not document abnormal shapes, internal corneal abnormalities, filtration angle abnormalities, microphakia or congenital cataracts, or microphthalmia or buphthalmia, which have been described previously in inherited anterior segment dysgenesis syndromes (21). We noted only incipient anterior and posterior cortical cataracts in several horses without multiple ocular anomalies, and only occasionally, in horses with ciliary cysts and iridal hypoplasia. The light microscopic sections of the hypoplastic uvea described by Ramsey et al (1) reveals a lack of iris dilator muscle. This muscle and the corpora iridica are derived from the neuroectoderm. Neuroectoderm may play a role in the development of the ocular anomalies of the Rocky

Mountain horse: the pathogenesis of inherited multiple ocular anomalies in horses warrants further investigation.

In conclusion, multiple ocular anomalies are prevalent in purebred and crossbred Rocky and Kentucky Mountain horses in Canada. This syndrome is inherited and the mode of inheritance is dominant with incomplete penetrance and it appears to be linked to coat color. The pathogenesis and mutation responsible for this syndrome are unknown.

Authors' contributions

Dr. Grahn was the major contributor of the clinical analysis, the pedigree development, and the writing of the manuscript. Dr. Pinard was responsible for collecting the clinical data on the Kentucky Mountain Horse herd, and collaborating with Dr. Sandemeyer in regards to the congenital ocular anomalies in the Rocky Mountain horses in western Canada. Drs. Bellone, Forsyth, and Sheila Archer, were part of our genetics investigation team and their expertise was used in regards to the pedigree development and the coat color association with the multiple ocular anomalies noted in the Rocky Mountain herd during the preparation of the manuscript.

Acknowledgments

The authors thank Jennifer Cowell and Claudia Pequin for their assistance in the development of the pedigree. CVJ

References

- Ramsey DT, Ewart SL, Render JA, Cooke CS, Latimer CA. Congenital ocular abnormalities of Rocky Mountain horses. *Vet Ophthalmol* 1999;2:47–59.
- Ramsey DT, Hauptman JG, Petersen-Jones SM. Corneal thickness, intraocular pressure, and optical corneal diameter in Rocky Mountain horses with cornea globosa or clinically normal corneas. *Am J Vet Res* 1999;60:1317–1321.
- Ewart SL, Ramsey DR, Xu J, Meyers D. The horse homolog of congenital aniridia conforms to codominant inheritance. *J Hered* 2000;91:93–98.
- Bedford PGC. Diseases and surgery of the canine eyelid. In Gelatt KN, ed. *Veterinary Ophthalmology*. 3rd ed. Philadelphia; Lippincott Williams and Wilkins 1999:535–568.
- Brunberg E, Andersson L, Cothran G, Sandberg K, Mikko S, Lindgren G. A missense mutation in PMEL17 is associated with the silver coat color in the horse. *BMC Genet* 2006;7:46.
- Reissmann M, Bierwolf J, Brockmann GA. Two SNPs in the SILV gene are associated with silver coat colour in ponies. *Anim Genet* 2007;38:1–6.
- Gotz W. Transgenic models of eye malformations. *Ophthalmic Genet* 1995;16:85–104.
- Yang LL, Lambert SR. Peter's anomaly: A synopsis of surgical management and outcome. *Ophthalmol Clin North Am* 2001;14:467–477.
- Alward WL. Axenfeld-Reiger syndrome in the age of molecular genetics. *Am J Ophthalmol* 2000;130:107–115.
- Lines MA, Kozlowski K, Walter MA. Molecular genetics of Axenfeld-Reiger malformation. *Hum Mol Gen* 2002;11:1177–1184.
- Williams DL. A comparative approach to anterior segment dysgenesis. *Eye* 1993;7:607–616.
- Churchill A, Booth A. Genetics of aniridia and anterior segment dysgenesis. *Br J Ophthalmol* 1996;80:669–673.
- Irby NL, Aguirre GD. Congenital aniridia in a pony. *J Am Vet Med Assoc* 1985;186:281–283.
- Peiffer RL, Belkin P. Keratolenticular dysgenesis in a kitten. *J Am Vet Med Assoc* 1983;182:1242–1243.
- Rebhun W. Congenital anterior staphyloma with rudimentary lens in a calf. *J Am Vet Med Assoc* 1977;171:440–442.
- Lewis D, Kelly D, Sansom J. Congenital microphthalmia and other developmental ocular anomalies in the Doberman. *J Small Anim Pract* 1986;27:559–566.
- Halenda RM, Grahn BH, Sorden SD, Collier LL. Equine congenital glaucoma: Clinical and light microscopic findings in two cases. *J Vet Comp Ophthalmol* 1997;7:105–109.
- Cullen CL, Grahn BH. Congenital glaucoma in a llama (*Llama glama*). *J Vet Comp Ophthalmol* 1997;7:253–257.
- Renker LW, Silversides DW, Xu Li, Overbeek PA. Formation of corneal endothelium is essential for anterior segment development — a transgenic mouse model of anterior segment dysgenesis. *Development* 2000;127:533–542.
- Cook CS. Ocular embryology and congenital malformations. In Gelatt KN, ed. *Veterinary Ophthalmology*, 3rd ed. Philadelphia; Lippincott Williams and Wilkins 1999:3–30.
- van Heyningen V. Developmental eye disease—a genome era paradigm. *Clin Genet* 1998;54:272–282.