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Equine Multiple Congenital Ocular Anomalies (MCOA) syndrome in *PMEL17* (Silver) mutant ponies: five cases

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Abstract

Objective—To describe the clinical phenotype and genetics of equine Multiple Congenital Ocular Anomalies (MCOA) syndrome in *PMEL17* (Silver) mutant ponies.

Animals studied—Five presumably unrelated ponies.

Procedures—The ponies were examined under field conditions in their barn by slit lamp biomicroscopy, indirect ophthalmoscopy, and applanation tonometry. Blood was collected and genomic DNA extracted for *MCOA* genotyping using the *PMEL17ex11* marker.

Results—One pony solely presented with temporal ciliary body cysts, suggestive of the less severe *Cyst* phenotype of MCOA; the animal was heterozygous at the *MCOA* locus. Multiple bilateral anterior segment anomalies were identified in four ponies, consistent with the more severe *MCOA* phenotype characterized by cornea globosa, iris hypoplasia, encircling granula iridica along the pupillary ruff, and cataracts. These animals were homozygous for the mutant *MCOA* allele. Four of the ponies had a silver dapple or chocolate coat color with white or flaxen manes and tails. Silver dappling was masked by the palomino coloring of a 5th pony that was homozygous at the *MCOA* locus.

Conclusions—The MCOA syndrome can be seen in ponies. The results of both clinical evaluation and genotyping resembled the previously described MCOA of both Rocky Mountain and Kentucky Mountain Saddle horses.

Keywords

anterior segment dysgenesis; equine multiple congenital ocular anomalies; MCOA; *PMEL17*; pony; silver dapple

INTRODUCTION

The equine Multiple Congenital Ocular Anomalies (MCOA) syndrome consists of various combinations of clinical symptoms predominantly affecting the anterior segment of the eye, including cornea globosa, uveal cysts, and iris hypoplasia. The syndrome has been well described in both Rocky Mountain and Kentucky Mountain Saddle horses, where it typically

affects animals with a silver coat color.^{1,2} Equine MCOA has also been observed in other breeds, including the Mountain Pleasure horse (derived from the same founder as Rocky Mountain and Kentucky Mountain horses), Morgan horse, ponies and miniature breeds.¹ However, to the best of our knowledge, a formal description of MCOA in ponies does not exist. Ponies are defined as horses of various breeds with adults measuring <14.2 hands or 147 cm at the withers.³ Here, we describe the occurrence of MCOA in five presumably unrelated ponies, and we propose the same mode of inheritance, and association with the *Silver* mutation and coat color, as in the MCOA of Rocky Mountain horses.

MATERIALS AND METHODS

The five ponies were independently examined at the farms where they were stabled in the states of California (1), New Jersey (2), New York (1), and Pennsylvania (1). Anterior segments were examined with diffuse and focal illumination using portable hand-held slit-lamp biomicroscopes (Kowa SL14; Kowa Company, Tokyo, Japan, and Kowa SL15; Kowa Optimed, Torrance, CA, USA). Fundic examinations were performed with portable binocular indirect ophthalmoscopes (Keeler All Pupil II; Keeler Instruments, Broomall, PA, USA) and condensing lenses (Double Aspheric 14D and 15D, Pan Retinal 2.2D, Digital ClearField, and Digital ClearMag; Volk Optical, Mentor, OH, USA). The Schirmer tear test I (Schering-Plough Animal Health, Union, NJ, USA) was used to measure aqueous tear production in one pony. Intraocular pressures were measured by applanation tonometry (TonoPen XL; Mentor, Norwell, MA, USA, and Tono-Pen Vet; Reichert, Depew, NY, USA) following the application of ocular surface anesthetic (0.5% proparacaine HCl ophthalmic solution). One animal was examined by ocular B-scan ultrasonography with a 10-MHz probe (VuMax; Sonomed, Inc., Lake Success, NY, USA).

In addition to the ophthalmic evaluation, whole blood was collected in tubes with EDTA from each pony and genomic DNA was extracted using the QIAmp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA) according to the manufacturer's protocol. Previously published primers surrounding the *PMEL17ex11* marker were used for PCR amplification (Table 1; Integrated DNA Technologies, Coralville, IA, USA).⁴ Each of the two forward primers was combined with each of the three reverse primers (total = 6 PCR products) to cover the region of interest with multiple PCR products and for DNA sequencing redundancy. The amplified products were gel purified using the QIAquick Gel Extraction Kit (Qiagen, Valencia, CA, USA) according to the manufacturer's protocol. The products were then sequenced with both forward and reverse PCR primers at the University of Pennsylvania DNA Sequencing Facility (ABI 3730XL and ABI 3100 Genetic Analyzers; Applied Biosystems, Foster City, CA, USA). The sequences were evaluated for the presence or absence of the cytosine (C; *wildtype*) to thymine (T; *Silver*) missense mutation at the 5th base within exon 11 of the *PMEL17* (*Silver*) gene using SEQUENCHER 3.1.1 software (Gene Codes, Ann Arbor, MI, USA).⁴ This mutation is responsible for the silver dapple coat color and a marker for MCOA (*PMEL17ex11*).^{4,5}

RESULTS

Case 1

An approximately 23-year-old Shetland pony gelding was presented for cataract evaluation because the owner noticed that the pony was visually impaired under dim light conditions. There was no information about pedigree or prior medical history. The animal had a silver dapple coat color with a white mane and tail (Fig. 1a). The ophthalmic examination revealed bilateral positive menace responses and dazzle reflexes. Both pupils were miotic with decreased pupillary light reflexes. Overall, the findings were identical for both eyes (OU), except for a ventral strabismus that was only present on the left side (Fig. 1b). Testing of the

optokinetic reflexes ruled out muscle paresis as the cause of ventral strabismus. Intraocular pressures were normal at 19 mmHg in the right eye (OD) and 20 mmHg in the left eye (OS). The corneas of this pony protruded excessively, and slit-lamp biomicroscopy revealed abnormally deep anterior chambers, confirming the presence of bilateral cornea globosa (Fig. 1c,d,e). Pharmacologic mydriasis was not achieved with application of either tropicamide or atropine sulfate 1% and the pupils remained miotic (Fig. 1f). The persistent bilateral miosis was not caused by anterior uveitis or prior drug applications. A diagnosis of iris hypoplasia was presumed based upon decreased pupillary light reflexes, and the lack of pupil dilation following topical application of mydriatics. The granula iridica encircled both miotic pupils through which nuclear cataracts were clearly distinguishable (Fig. 1f). Only the most peripheral parts of the ocular fundi could be appreciated by indirect ophthalmoscopy and they appeared unremarkable. The combination of bilateral cornea globosa, iris hypoplasia, and nuclear cataracts in a silver dapple pony was most consistent with MCOA (Table 2).^{1,2,5,6} The pathogenesis of the ventral strabismus of the left globe was not determined.

Case 2

An approximately 4-year-old pony mare was examined following acquisition from an auction. Prior medical history and breed information was unknown. The owners did not observe any ocular abnormalities or signs of visual deficits. The pony had a chocolate-colored coat, with faint to absent dapppling, and a flaxen-colored mane and tail (Fig. 2a). Examination of the anterior and posterior segments was unremarkable except for cysts arising from the lateral ciliary body OU (Fig. 2b). The pupils dilated normally following the topical application of tropicamide 1% ophthalmic solution. The combination of anterior uveal cysts and diluted hair color was most consistent with the *Cyst* phenotype of MCOA, as previously described in Rocky Mountain horses (Table 2).^{1,2,5,6}

Case 3

An approximately 35-year-old Shetland pony gelding was presented with blindness and right eye cloudiness with intermittent epiphora. A detailed medical history and pedigree were not available. The pony had been previously diagnosed with Cushing's disease (hyperadrenocorticism) but was not receiving any medication for the condition. Prior episodes of laminitis had resolved. The pony was silver dapple in color (Fig. 3a,b). Menace responses, pupillary light, and dazzle reflexes were not present OU. The right eye was buphthalmic with diffuse corneal edema and superficial corneal neovascularization (Fig. 3c,d). Intraocular structures could not be examined in detail OD due to the severity of the corneal edema. However, the right pupil was dilated with diffuse goniosynechiae, and the right lens was cataractous (Fig. 3d). There was a ventral strabismus on the left side (Fig. 3c,e). Muscle paresis was not the cause for the ventral strabismus based upon normal optokinetic reflexes. The left pupil was dilated and nonresponsive, and there was a diffuse immature cataract (Fig. 3e). The ocular fundi could not be examined due to the cataracts OU and the severe corneal edema OD. Both eyes did not stain with fluorescein. Intraocular pressures as measured by applanation tonometry were slightly elevated at 32 mmHg OD and 29 mmHg OS. There were no obvious clinical signs of chronic uveitis OU.

Both eyes were treated with topical dorzolamide/timolol combination ophthalmic solution 2–3 times daily to address the elevated intraocular pressures. After 14 days the pony was re-examined. Intraocular pressures had reduced to 18 mmHg OU, and the right cornea was less edematous as appreciated by slit-lamp biomicroscopy. Otherwise, the results of the ophthalmic examination were the same as 2 weeks earlier. At the time of manuscript submission, the pony's eyes were maintained on the topical medication for over 1 year. The clinical signs seen in this animal are commonly acquired anomalies in horses with chronic,

recurrent anterior uveitis.⁷ Because of the pony's coat color, MCOA was considered as a differential diagnosis (Table 2). The lack of previous ophthalmic examination data prevented the unequivocal determination of the pathogenesis. The presumed secondary chronic ocular hypertension may have caused damage to the retina and optic nerve resulting in blindness. The reason for the ventral strabismus of the left globe was also not determined.

Case 4

A 7-year-old silver dapple pony stallion initially presented with a painful right eye due to a superficial corneal stromal abscess. The pony had a white mane and tail (Fig. 4a). The abscess did not respond to medical therapy. Subsequently, a superficial keratectomy was performed to remove the abscess, and a conjunctival pedicle graft was placed on the exposed corneal stroma (Fig. 4b). Aerobic and fungal culture did not produce any viable organisms. Topical and systemic medical therapy was continued, and the cornea healed without complication. The treatment included the use of topical atropine sulfate 1% solution for iridocycloplegia, but the pupil did not dilate. Over the following 1.5 years, the pony's right eye was intermittently treated topically with ophthalmic flurbiprofen 0.03% and atropine sulfate 1% solutions as well as systemically with oral flunixin meglumine because of recurrent episodes of mild ocular discomfort. The animal remained sighted OU.

Simultaneously to the diagnosis and treatment of the right corneal stromal abscess, abnormally protruded corneas with deep anterior chambers (cornea globosa) and immature cortical cataracts were observed OU; the right lens was subluxated (Fig. 4b,c). Both irides appeared hypoplastic, with miotic pupils that were minimally responsive to light and unresponsive to topical atropine sulfate; the granula iridica were flattened and encircled the pupils (Fig. 4b). Schirmer tear tests (22 mm/min OU) and intraocular pressures (multiple measurements over 2 years averaged 25–29 mmHg OU) were normal after the right cornea had healed. The regions of the ocular fundi that could be visualized through the cataractous lenses appeared unremarkable. Ocular B-scan ultrasonography did not reveal any additional anomalies. The clinical findings in this silver dapple pony were most consistent with MCOA (Table 2).^{1,2,5,6}

Case 5

An approximately 25-year-old Shetland pony gelding presented for blepharospasm and epiphora OS. He was a palomino with dappling (Fig. 5a). The owner also commented that the pony's vision was abnormal, especially into the distance. The animal was receiving medication for the previously diagnosed Cushing's disease (hyperadrenocorticism). Positive fluorescein staining revealed the presence of a superficial corneal ulcer OS associated with mild corneal edema and several bullae. The right cornea had central stromal fibrosis from a previous injury. The pony had normal menace responses OU, but both pupils were miotic, nonresponsive to light, and could not be dilated with topical tropicamide 1%, or with the combination of tropicamide and phenylephrine HCl 10% ophthalmic solutions. There was no evidence of posterior synechiae. Furthermore, the granula iridica appeared flattened and were circumferentially oriented at the pupillary ruff (Fig. 5b,c). Despite the small pupil size mild anterior cortical and nuclear cataracts were visible in both eyes (Fig. 5b,c). Only a limited view of the posterior segments was possible, but there were no obvious abnormalities. Applanation tonometry indicated normal intraocular pressures of 21 mmHg OU.

Treatment of the ulcerative keratitis and corneal edema with mild bullae OS consisted of neomycin-polymixin B-bacitracin, sodium chloride 5%, and atropine sulfate 1% ophthalmic ointments. At a 5-day recheck the corneal ulcer and bullae had healed, and the blepharospasm and epiphora had resolved. Intraocular pressures were 21 mmHg OD, and 22

mmHg OS. Despite three applications of atropine sulfate ophthalmic ointment miosis of the left pupil persisted. To rule out treatment inconsistency atropine sulfate 1% ophthalmic solution was applied to each eye. The pupils failed to dilate, which was consistent with iris hypoplasia. The combination of iris hypoplasia, flattened granula iridica, and cataracts was most consistent with MCOA (Table 2).^{1,2,5,6}

Genotyping

The results of the *PMEL17ex11* genotyping are shown in the chromatograms of Fig. 6. The sequences were evaluated for the presence or absence of the C (*wildtype*) to T (*Silver*) missense mutation of the 5th nucleotide within exon 11 of the *PMEL17* (*Silver*) gene. This *Silver* mutation is responsible for the silver dapple coat color and at the same time a marker for MCOA.⁴ Cases 1, 3, 4, and 5 were homozygous for the mutant MCOA allele as indicated by a single T-peak in their chromatograms (Fig. 6) (Table 2). Case 2 was heterozygous with overlapping peaks for C and T (Fig. 6) (Table 2). Both homozygous and heterozygous animals have a silver or chocolate coat color because the *Silver* mutation is inherited as an autosomal dominant trait.⁴ Exceptions to this mutation's effect on coloration are found in red horses, such as chestnuts and palominos (for example case 5), that do not express eumelanin.^{4,8} Heterozygous horses manifest with the milder *Cyst* phenotype of MCOA whereas homozygous animal present with multiple anterior segment anomalies.⁵

DISCUSSION

Equine MCOA syndrome is characterized by the presence of temporal anterior uveal cysts with or without a combination of other anterior segment anomalies.^{1,2,6} It has been previously described in both Rocky Mountain and Kentucky Mountain Saddle horses.^{1,2,5} The condition was initially named Anterior Segment Dysgenesis (ASD) but it has been more appropriately termed as MCOA.^{1,2} Equine MCOA has been appreciated in other breeds including Morgan Horses, Belgian Draft horses, ponies and miniatures.¹ However, to the best of our knowledge, our finding is the first formal documentation of the condition in ponies. We have presented five presumably unrelated ponies with clinical signs resembling the MCOA of affected Rocky Mountain horses.

The most common symptom of MCOA is the presence of temporal cysts of the posterior iris, ciliary body, and peripheral retina.^{1,2,6} The retinal cysts are considered extensions of uveal cysts and may manifest as retinal dysplasia or retinal detachment.¹ If these cysts are the only ocular anomalies in an animal, the clinical findings are classified as the less severe *Cyst* phenotype of equine MCOA.^{1,2,6} Horses with the *Cyst* phenotype appear normal and are unlikely to be identified, except inadvertently, by their owners or veterinarians. In case 2, cysts were only discovered during a routine health check. Horses are classified as having the more severe *MCOA* phenotype if the temporal ciliary cysts are combined with other congenital ocular anomalies, including cornea globosa, iridocorneal angle abnormalities, iris hypoplasia, cataracts, lens subluxation, or macropalpebral fissure and craniofacial abnormalities.^{1,2,6} In four of our ponies, the ophthalmic findings were consistent with the *MCOA* phenotype. Although undocumented, we suspect that in some of these animals temporal uveal cysts were present but not visible under field conditions. Ocular ultrasonography might reveal these cysts.

While cataracts and lens luxations in adult horses are most commonly caused by chronic uveitis,⁹ we suspect that these abnormalities were part of the MCOA phenotype in cases 1, 4, 5 and possibly even 3.^{2,10} Subjectively, we did not perceive any enlargement of the palpebral fissures (macroblepharon) in any of our animals.^{2,10}

One pony's glaucoma (case 3) could have been a consequence of MCOA-associated goniosynechia, especially since the animal was homozygous at the *MCOA* locus. While equine MCOA is generally considered a nonprogressive condition,^{1,2,5} chronic glaucoma may have caused visual loss and corneal disease in this case. In the same pony, iris hypoplasia could have been masked by glaucoma-induced mydriasis.¹¹ In general, equine glaucoma is most commonly a complication of chronic anterior uveitis in adult horses,¹¹ a possibility that we could not rule out in case 3 even with the suspected presence of MCOA. We believe that the corneal stromal abscess and ulcers seen in cases 4 and 5 were unlikely to be related to MCOA.

We could not associate the ventral strabismus in the left eyes of two ponies with MCOA. The strabismus could have been congenital or acquired. Acquired abnormalities in the visual axes of horses are typically caused by severe head trauma with skull fractures or central nervous system infections.¹² There were no other clinical signs supporting a prior trauma or extraocular muscle palsy. It is possible, but rather unlikely, that in these ponies a misrouting of optic nerve fibers was responsible for the strabismus. This phenomenon has been previously described in color-dilute Siamese cats.¹³

Similar to the Rocky Mountain and Kentucky Mountain Saddle horses,^{2,10} we found an association between MCOA and the diluted silver or chocolate coat color, with white or flaxen-colored manes and tails. The silver coat color is characterized by dilution of the black pigment eumelanin.⁴ The gene mutation responsible for the silver coat color has recently been identified as a missense mutation in exon 11 of the *Silver* or *PMEL17* gene on equine chromosome 6 (ECA6q23).^{4,14} *PMEL17* encodes the pre-melanosomal protein 17 (PMEL17), a transmembrane protein of melanosomes that plays an important role in the formation of the characteristic fibrillar structure of these organelles.^{15,16} The exchange of a single nucleotide from C to T within exon 11 leads to a missense change of the second amino acid of PMEL17's cytoplasmic region from an arginine to a cysteine (Arg618Cys).⁴ This mutation in *PMEL17* leads to a dilution or inhibition of the black pigment eumelanin, but does not affect the synthesis of the red pheomelanin.^{16–18} Black and bay horses become silver dappled, but chestnut and palomino horses (such as case 5) are unaffected because they do not express eumelanin.⁴ Similar hypopigmented phenotypes have been described in *PMEL17*-mutant chickens and mice.^{4,17,18} In dogs, a mutation in *PMEL17* results in the merle coat color, characterized by patches of diluted pigment intermingled with normal melanin.^{19,20}

The silver coat color of horses is inherited as an autosomal dominant trait with color dilution in both homozygous and heterozygous animals.⁴ Homozygous animals may be more color diluted than heterozygotes,⁴ consistent with a darker coat color and underappreciated dappling, as seen in our heterozygous case 2. The other ponies in this study were homozygous for the *Silver* mutation and therefore more color dilute with clearly visible dappling. The exception was case 5 with the palomino coat color that masked the effect of the *Silver* mutation.

It has recently been shown that the missense mutation in *PMEL17* (*Silver*) showed complete linkage with the *MCOA* locus in Rocky Mountain horses and therefore serves as a genetic marker (*PMELex11*) for MCOA.⁵ The *MCOA* locus has been narrowed to a 4.9 megabase (Mb) interval on the equine chromosome 6 (ECA6q) that includes the *PMEL17* gene.⁵ The close proximity of the *PMEL17* gene to the *MCOA* locus explains why coat color appears to be linked to the expression of ocular anomalies.⁵ The mutated *PMEL17* (*Silver*) gene is presumably linked with the unknown mutated *MCOA* gene, and the wildtype *PMEL17* gene is similarly linked with the wildtype form of the *MCOA* gene. Both the *Silver* mutation and the *MCOA* mutation are dominantly inherited traits, but there is incomplete penetrance for

the *MCOA* mutation.² This means that a heterozygous animal will always be a silver dapple but is less severely affected by MCOA with only uveal cysts (*Cyst* phenotype).^{2,5,6} A homozygously affected animal will be a silver dapple and have multiple anterior segment anomalies (*MCOA* phenotype). Even though we did not have any pedigree information for our ponies, the genotyping allowed us to confirm the same inheritance pattern as in Rocky Mountain horses. Multiple bilateral abnormalities (including cornea globosa, iris hypoplasia, and nuclear cataracts) were identified in cases 1, 3, 4, and 5, consistent with the *MCOA* phenotype. These animals were homozygous for the mutant *MCOA* allele (Table 2). In case 3 the diagnosis was not unequivocal since all the ocular anomalies could also have been acquired. It is remotely possible that case 3 was not affected by MCOA despite being homozygous for the in *PMEL17* (*Silver*) mutation; a scenario that could be explained by recombination events between the *PMEL17* (*Silver*) and the *MCOA* genes. Case 2 presented only with temporal ciliary body cysts, which was suggestive of the *Cyst* phenotype and associated with a heterozygous *MCOA* genotype (Table 2).

Despite the explanations in the previous paragraph, the *PMEL17* (*Silver*) mutation has not been excluded as the causative gene for MCOA.⁵ Our case series supports the notion that the (still unknown) *MCOA* gene and the *PMEL17* (*Silver*) gene are the same, or at least overlap on ECA6q23. Mutations in *PMEL17* have also been associated with an abnormal ocular phenotype of zebrafish known as the fading vision mutation (*fdv*).²¹ Canine merle coat coloration has also been associated with ocular defects including coloboma, and microphthalmia.^{22,23} However, there have been indications in horses about a dissociation of the *PMEL17* and *MCOA* mutations by recombination: for example, MCOA-like abnormalities have not been seen in some *PMEL17* mutant horses, including some silver-colored Icelandic ponies^{1,2,5,6,10} and possibly our case 3, and a few nonsilver dapple horses have expressed the *MCOA* phenotype.^{1,2,5,6,10}

The prevalence of MCOA in purebred and crossbred Rocky Mountain and Kentucky Mountain horses has been estimated to be ~50% of their populations.^{1,2} This relatively high incidence of MCOA may be a founder effect based on the popularity of silver-colored horses.^{1,2,4-6} The breeding of individuals with desired characteristics (silver dapple) propagated an undesirable linked trait (MCOA). We suspect that any breed with a high frequency of silver-colored animals will be associated with an increased incidence of MCOA due to this linkage. The percentage of ponies with MCOA still needs to be determined.

CONCLUSIONS

We present here the first formal report of equine MCOA syndrome in ponies. We show that both the clinical phenotypes and the genetics of the condition in ponies are in agreement with the previously published findings for Rocky Mountain and Kentucky Mountain horses. MCOA is inherited as an autosomal dominant trait with incomplete penetrance. Homozygous ponies showed multiple congenital anterior segment anomalies, whereas a heterozygous pony only presented with temporal uveal cysts. Because of close linkage the *PMEL17* or *Silver* mutation currently serves as one possible genetic marker for MCOA.

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Figure 1.

Case 1. (a) A 23-year-old pony gelding with a black and silver coat color with dappling, and a white mane and tail. (b) The left globe with a ventral strabismus. Both the right (c) and left corneas (d) were protruding with resultant deep anterior chambers (cornea globosa). (e) A normal control eye of an unrelated horse is shown for comparison of the corneal curvature. (f) The pony exhibited bilateral iris hypoplasia, encircling granula iridica along the pupillary ruff, and nuclear cataracts.

Figure 2.
Case 2. (a) A young pony mare with a chocolate-colored coat, very faint dappling, and a flaxen-colored mane and tail. (b) Ocular abnormalities consisted of temporal multiloculated uveal cysts (arrows) appreciated after pharmacologic mydriasis.

Figure 3.

Case 3. (a) A blind silver dapple pony with white mane and tail. (b) Detailed view of dappling. (c) The right buphthalmic eye with diffuse corneal edema, and the left eye with a ventral strabismus. (d) A close-up of the right eye revealing diffuse corneal edema and neovascularization, as well as the goniosynechiae (arrows). (e) The mydriatic left pupil with a cataractous lens.

Figure 4.

Case 4. (a) A 7-year-old pony stallion with silver dapple coat color including a white mane and tail. The animal was affected by the more severe *MCOA* phenotype, which included (b) iris hypoplasia, flattened and encircling granula iridica, cataracts, and (c) corneal globosa. A conjunctival pedicle graft is visible on the right cornea 3 years after surgery (b).

Figure 5.

Case 5. (a) Even though this 25-year-old palomino Shetland pony gelding was homozygous for the *PMEL17* (*Silver*) mutation, it did not show the silver coat color. Eumelanin expression is blocked in palomino horses, which masks the phenotypic effect of the *PMEL17* mutation. (b,c) Both eyes showed multiple anterior segment anomalies, including iris hypoplasia, flattened and circumferentially oriented granula iridica, and cataracts.

Figure 6.

PMEL17ex11 genotyping. The chromatograms show the variations in the DNA sequence at the critical site (gray shading) of exon 11 within the *PMEL17* (*Silver*) gene. A normal, nonsilver control horse is homozygous for the wildtype allele with cytosine (C) at the critical location. For comparison, a color-dilute, silver Rocky Mountain horse with multiple congenital ocular anomalies is homozygous for the mutant allele with thymine (T) at the critical site. The chromatograms show that cases 1, 3, 4, and 5 were also homozygous for the mutant allele with T. Only case 2 was heterozygous with both a C and a T at the same location.

Table 1PCR primers used for genotyping *PMEL17ex11* (4)

Forward primers	Reverse primers
5'-GCA GGG AAG CTT GTA GAG TGA-3'	5'-CTC TCA CCA AAG GGG GAA G-3'
5'-AGA GGC AGG CCT TGG GCA G-3'	5'-TGC TCT CAC CAA AGG GGG AAG-3'
	5'-AGG GAA GAC TGG AGA CAA GA-3'

Nucleotides: A, adenine; T, thymine; G, guanine; C, cytosine.

Table 2

Summary of clinical phenotypes and genotypes

Case	Cornea globosa	Iris hypoplasia	Uveal cysts	Cataract	Phenotype	Genotype <i>PMEL1/ex11</i> marker
1	+	+	ND	+	<i>MCOA</i>	T/T homozygous
2	–	–	+	–	<i>Cyst</i>	T/C heterozygous
3	–	ND	ND	+	Possible <i>MCOA</i>	T/T homozygous
4	+	+	–	+	<i>MCOA</i>	T/T homozygous
5	+	+	ND	+	<i>MCOA</i>	T/T homozygous

+, present; –, absent; ND, no data.

MCOA, severe multiple congenital ocular anomalies phenotype; *Cyst*, mild *Cyst* phenotype.

Nucleotides: T, thymine; C, cytosine.