Clinical Commentary

Multiple congenital ocular anomalies and the silver dapple gene

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Although descriptions of familial trends in cases of ocular disease in horses occur relatively commonly in the literature (Petersen-Jones and Ewart 2011), this has often been anecdotal and authenticated genotypic or haplotypic linkage to ocular disease has only infrequently been reported. Examples include congenital stationary night blindness, equine recurrent uveitis and multiple congenital ocular anomalies (MCOA). Multiple congenital ocular anomalies syndrome is of particular interest in that linkage of the disease phenotype with coat colour genotype has been forensically investigated using state of the art gene technologies, providing a window into a future where a dynamically progressive understanding of genotypic influences on disease becomes possible. Multiple congenital ocular anomalies, initially described as anterior segment dysgenesis, was first identified in Rocky Mountain horses (RMH), with over 50% of 514 animals in the study population being affected to some degree (Ramsey et al. 1999). The RMH breed was established in the late 19th century, and the preferred coat colour phenotype is described as ‘chocolate with a flaxen mane and tail’ (Lynghaugh 2009). This ‘silver’ or ‘silver dapple’ coat colour represents expression of a premelanosomal protein 17 gene mutation (PMEL17), known as the silver dapple gene, on a background black coat colour (Brunberg et al. 2006), and linkage of the silver dapple coat colour with the MCOA dysgeneses in the RMH came under early suspicion. A probable pleiotropic linkage of a mis-sense mutation in the PMEL17 gene, present on equine chromosome 6, with expression of the MCOA phenotype in the probands was thought likely (Brunberg et al. 2006). This hypothesis was strengthened by linkage analysis mapping of a small region of chromosome 6 in the RMH, which demonstrated linkage disequilibrium, based on a 4.9 megabase interval linkage, between the MCOA locus and 3 candidate gene markers, including PMEL17 (Andersson et al. 2008). Phenotypic linkage of MCOA with the silver dapple coat colour has now been identified in other breeds, including the RMH-related Kentucky Mountain horse (Grahn et al. 2008) and the unrelated Icelandic horse (Andersson et al. 2011a) and American Miniature horse (Plummer and Ramsey 2011), although the frequency of expression of the silver coat phenotype is lower in these breeds than in the RMH (Andersson et al. 2008). Andersson et al. (2011b) further narrowed the interval between the MCOA locus and the mutant PMEL17 gene in these breeds, giving greater credence to haplotypic association of MCOA with the PMEL17 mutation. MCOA has also been described in Mountain Saddle horses (Grahn et al. 2008), Belgian Draft horses (Andersson et al. 2011b), Comptois horses (Depecker et al. 2013), European Shetland and Deutches Classic ponies (Premont et al. 2013) and in mixed breed ponies in the US (Komaromy et al. 2011). Testing for the mutant PMEL17 gene in these populations has shown that MCOA is linked both phenotypically and haplotypically to the silver coat colour.

The MCOA model corresponds to a codominant mode of inheritance, with homozygous phenotypes expressing a spectrum of overt, mainly anterior segment, ocular dysgeneses and heterozygous phenotypes expressing relatively innocuous posterior segment pathology. The possibility of incomplete or nonpenetrance of the mutant gene, where no ocular abnormality is expressed, has been alluded to (Ewart et al. 2000) and a possible incidence of 6% nonpenetration in heterozygous carrier horses has been discussed (Andersson et al. 2011b). However, as recognised by Andersson and her colleagues, this could, in some instances at least, reflect difficulties in the clinical diagnosis of minor ocular pathology in heterozygous carriers, with the potential to lead to overestimation of the frequency of incomplete or nonpenetrance (Segard et al. 2013). The homozygous phenotype, usually referred to as the MCOA phenotype, shows severe and multiple anterior and posterior segment dysgeneses. These include megalocornea and cornea globosa, iris hypoplasia and temporal iridocorneal goniosynechae and iridociliary cysts (Ramsey et al. 1999; Wilkie 2011). Congenital cataract is common. Posterior segment dysgeneses include temporal peripheral retinal and iridociliary cysts and retinal dysplasia and detachments (Wilkie 2011). Multiple congenital ocular anomalies phenotype horses variably express these dysgeneses, but typically are bilaterally and symmetrically affected. Multiple congenital ocular anomalies horses usually have slow pupillary light responses, in part likely to be a consequence of the iridial hypoplasia commonly present in affected eyes. However, despite the severity of the retinal pathology frequently present and the astigmatic effect of abnormal corneal contour, affected horses rarely appear to show behavioural evidence of visual dysfunction (Ramsey et al. 2000).

The heterozygous phenotype is referred to as the cyst phenotype. In these animals the primary presenting pathology is multiple posterior ciliary or peripheral retinal cysts, typically located temporally (Fig 1). In some cases associated peripheral retinal detachments may be identified. Recently Segard et al. (2013) have shown that cysts were identified ultrasonographically in 70% of Comptois horses and RMHs heterozygous for the PMEL17 mutation, yet which had no abnormality detectable on direct ophthalmoscopy. The significance of this observation is clear; incomplete penetrance of the mutant gene may be present in some of these horses (Andersson et al. 2011b; Petersen-Jones and Ewart 2011); however, it seems the case that some heterozygous cyst phenotypes are simply clinically undetectable unless detailed ultrasonography is employed.

Clearly, it is desirable on general principles that a process of eliminating the mutant PMEL17 gene from the equine gene pool should begin. However, given the aesthetic preference for silver coat colour, which in many ways defines some of the affected breeds and the relatively high frequency of
expression of the mutant gene in the at risk population, it is likely that this is not going to be achieved other than in the very long term. That the silver dapple mutant genotype (PMEL17) may not be phenotypically apparent in carrier animals lacking a black base coat colour is likely to be a significant complication in any breeding programme where preliminary screening on the basis of coat colour phenotype, and without gene testing, is instituted (Andersson et al. 2011b). However, identifying carrier animals by ophthalmic examination, including ultrasonography, and confirming their carrier status by gene linkage testing with a view to progressively reducing the incidence of MCOA in the horse population by a structured breeding programme should be considered. At a more practical level (Fig 1), owners of silver or silver dapple animals should be advised of the possible consequences of breeding with similar coat colour animals, these consequences being the possible birth of MCOA phenotype foals and contributing to maintaining a deleterious mutant gene in the population.

Author’s declaration of interests
No conflicts of interest have been declared.

References


