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Lack of genetic association among coat colors, progressive retinal atrophy and polycystic kidney disease in Persian cats

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An inherited form of progressive retinal atrophy (PRA) is recognized in Persian cats; however, the prevalence of PRA in the breed has not been determined. Breeders suggest that cats from only brown ('chocolate') or Himalayan ('pointed') lines are at risk for PRA, suggesting the disease is not widespread. This study was designed to evaluate whether PRA in Persian cats is associated with three coat colors, including chocolate, or with a highly prevalent inherited disease in this breed – polycystic kidney disease (PKD). Sixty related cats were evaluated for PRA by ophthalmic examination and genetically typed for PKD and the mutations that cause coat color variants in agouti, brown and color (producing the pointed coloration in Himalayan). No associations were identified among any of the traits, including between PRA and chocolate. These data suggest that PRA is not limited to cats with chocolate coat coloration and breeders and veterinarians should be aware that the prevalence of the disease may be higher than currently claimed.

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P rogressive retinal atrophy (PRA) refers to a heterogeneous group of heritable retinopathies causing blindness in dogs and cats (Millichamp 1990, Sargan et al 1994). Forms of PRA have been described in domestic mixed breed (West-Hyde and Buyukmihci 1982), Persian (Rubin and Lipton 1973), and Abyssinian cats (Narfström 1983, Barnett and Curtis 1985). Two different forms of PRA in Abyssinian cats have been documented in Sweden (autosomal recessive, late onset PRA) and in UK (autosomal dominant, early onset PRA) (Narfström 1983, Barnett and Curtis 1985).

Recently, Rah et al (2005) described an autosomal recessive, early onset form of PRA in several independently-bred Persian cats from different regions of the United States. These cats comprised a breeding colony established to characterize this disease using cats donated to one of the authors (LAL). While the prevalence of PRA in 248 Abyssinian cats in the Netherlands was estimated as 4.4% (Djajadiningrat-Laanen et al 2002), the prevalence of PRA in other breeds or in other countries has not been reported. Selection by cat fancy breeders has led to grouping of Persian cats into Himalayan (ie, ‘pointed’ or colorpoint Persian cats) and non-Himalayan Persian cats. Additionally, many color variants of Himalayan cats have been developed including chocolate-pointed. Breeders have indicated that chocolate Persian or Himalayan cats are the only individuals at risk for PRA (K. Meeks and L. Shelton, personal communication). This anecdotal claim might disguise the true prevalence and risk of PRA in Persian and related breeds and lead to some cases being overlooked. Autosomal dominant polycystic kidney disease (PKD) and various coat colors, including non-agouti (non-tabby solid), temperature-sensitive albinism ('pointed'), and chocolate also segregate within the Persian breed (ie, the disease alleles can be followed in the pedigree and are concordant with the trait)
and genetic tests for these phenotypes exist. A mutation in the gene tyrosinase-related-protein-1 (TYRP1) causes the chocolate phenotype in cats (Lyons et al 2005a, Schmidt-Kuntzel et al 2005), and a missense mutation in the gene tyrosinase (TYR) causes the ‘pointed’ coat color phenotype that restricts coloration to mainly the extremities (face, ears, tails and paws), especially in the Himalayan and Siamese breeds of cats (Lyons et al 2005b, Schmidt-Kuntzel et al 2005). A deletion mutation in the agouti signaling protein (ASIP) gene is responsible for the non-tabby, solid coat color (Eizirik et al 2003). A mutation in gene PKD1 was reported to cause PKD in Persian cats (Lyons et al 2004). This information permitted us to evaluate by linkage analyses if any associations exist among PRA, coat color, and PKD in a group of cats that segregated for PRA and to critically assess the suggestion that chocolate or ‘pointed’ coat coloration is associated with PRA in Persian cats.

A breeding colony to investigate PRA was established using five (two males and three females) purebred Persian cats donated by breeders (Rah et al 2005). Historical pedigree data were provided by the owners and investigated using cat pedigree databases to establish kinship and to identify common founder cats (http://www.catpedigrees.com/calivan.shtml). Complete ophthalmic and neuro-ophthalmic examinations were performed by a board-certified veterinary ophthalmologist (DJM) to diagnose PRA. Details of these examination techniques are reported elsewhere (Rah et al 2005). Genetic typing for the three coat color variants (Eizirik et al 2003, Lyons et al 2005a, 2005b) and PKD (Lyons et al 2004) was performed as previously described. For all genetic typing, DNA was extracted from white blood cell preparations, from EDTA whole blood, and/or tissues by standard phenol/chloroform extractions (Sambrook and Russell 2001). Two-point likelihood ratio test (linkage analysis) between PRA and the conventional statistical value for rejection of association is an LOD score (Z) ≤ –2.0 (Ott 1999). The estimated recombination fraction (θ) at Z ≤ –2.0, provides the genetic distance that has been excluded as a possible location for the gene causing the phenotype of interest, in this case, PRA. Genetic distance, θ, is presented as morgans (M), which can be converted to an average physical distance in nucleotide bases (Haldane 1919, Donis-Keller et al 1987). Generally, 1 centimorgan (cM) is equivalent to 1 million bases (Mb), however, true distance conversions can be altered by neighboring nucleotide sequence and position on the chromosome (Donis-Keller et al 1987, Ott 1999). The most significant exclusion was estimated between PRA and ASIP, suggesting that the gene for PRA is not within 26 cM either side of the ASIP locus. Exclusion of PRA to TYRP1 (chocolate) and PKD extended to θ = 0.16 each, suggesting that PRA is not restricted some Persian cat breeding programs, and potentially restricted genetic variation in some lines of Persian cats (K. Meeks and L. Shelton, personal communication). Sixty cats from a multi-generational pedigree (Lyons et al 2005a, 2005b, Rah et al 2005) were assessed in this study. Based on historical pedigree data, the Persian cats represented three independent lines; one Himalayan line with chocolate coat coloration and two non-Himalayan, non-chocolate lines. The five founder Persian cats could be traced back to a common ancestor queen from a non-chocolate, non-Himalayan line born in the early 1960s. These data suggest that the PRA mutation did not originate in a chocolate or Himalayan line and that all Persians may be at risk for PRA. Additionally, based on the number of championship offspring produced by the identified common ancestor, it is likely that the common ancestor had a significant influence on the breed (L. Shelton, personal communication). This also suggests that the PRA mutation is likely to be widespread.

Based upon ophthalmic examination of all 60 cats, 28 were diagnosed with PRA. Twenty-six cats (10 with PRA) were diagnosed with PKD by genetic typing, 39 cats (17 with PRA) were classified as non-tabby solid, 17 (5 with PRA) as chocolate, and 25 (11 with PRA) as the ‘pointed’ coat type. Linkage analysis results are presented in Table 1. In the present study, linkage analysis showed no association between the PRA phenotype and three coat colors or PKD. Likewise, no associations were identified among any of the traits. The conventional statistical value for rejection of association is an LOD score (Z) ≤ –2.0 (Ott 1999). The estimated recombination fraction (θ) at Z ≤ –2.0, provides the genetic distance that has been excluded as a possible location for the gene causing the phenotype of interest, in this case, PRA. Genetic distance, θ, is presented as morgans (M), which can be converted to an average physical distance in nucleotide bases (Haldane 1919, Donis-Keller et al 1987). Generally, 1 centimorgan (cM) is equivalent to 1 million bases (Mb), however, true distance conversions can be altered by neighboring nucleotide sequence and position on the chromosome (Donis-Keller et al 1987, Ott 1999). The most significant exclusion was estimated between PRA and ASIP, suggesting that the gene for PRA is not within 26 cM either side of the ASIP locus. Exclusion of PRA to TYRP1 (chocolate) and PKD extended to θ = 0.16 each, suggesting that PRA is not
within $16\text{ cM}$ either side of each of these loci. The analysis between \textit{PRA} and the \textit{TYR} (‘pointed’) locus also showed exclusion extending to $\Theta = 0.025$. Therefore, although cat breeders generally appear well informed concerning basic inheritance of coat colors, our data suggest that allegations of an association between \textit{PRA} and the \textit{brown} locus are incorrect. This suggests that chocolate Persian cats are not genetically predisposed to a higher risk of developing \textit{PRA}. Rather, the risk should be more homogenous throughout the breed. Therefore, veterinarians should be aware that \textit{PRA} may be prevalent in the breed and indicate to Persian cat breeders that Persian cats of all coat colors are at risk for \textit{PRA}. In addition, current or historical use of Persian cats in breeding programs for other breeds, eg, Scottish Folds and American Shorthair cats, may have introduced \textit{PRA} into these breeds. Closely related breeds, such as the Exotic (‘Shorthair Persian’) cat, may also have a risk of developing \textit{PRA}. The infrequent reports of \textit{PRA} may be due to lack of awareness of the disease, selection by breeders, recent origin of the mutation or random loss (genetic drift) of the mutation in the Persian cat population.

This study also demonstrates the value of developing robust colonies of cats that co-segregate for various traits of interest. Although the pedigree was not intentionally bred for variations at the \textit{ASIP}, \textit{TYR}, \textit{TYRP1} and \textit{PKD} loci, these traits have assisted with the priorities of genome scanning for \textit{PRA}. Because no associations were identified among any of the traits investigated, exclusion of large regions on cat chromosomes A3, D4, and E3 where \textit{ASIP}, \textit{TYRP1} and \textit{PKD} are located, respectively, is possible. Therefore, these chromosomes could be given a lower priority in the gene-mapping strategy to locate the gene responsible for \textit{PRA} in Persian cats.

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### References


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