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Albinism in the domestic cat (Felis catus) is associated with a tyrosinase (TYR) mutation

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Summary

Albinism is a congenital disorder that is characterized by lack of pigment in hair, skin and eyes. Recently, the causative mutations for the siamese and burmese temperature-sensitive alleles have been identified in tyrosinase (TYR; Lyons et al. 2005). Complete albinism in cats is hypothesized to be caused by an additional allele at TYR, contributing to the allelic series at the colour (C) locus: C (full colour) > c\(^b\) (burmese) > c\(^b\) (siamese) > c (complete albino). To confirm that albinism is a TYR allele in cats, an analysis of an Oriental and Colourpoint Shorthair cat pedigree that segregates for albinism (Fig. 1) was tested for linkage with FCA931, a marker ~1.7 cM from TYR (Menotti-Raymond et al. 1999, 2003). In addition, sequence analyses of TYR were conducted to identify a causative mutation for feline albinism.

DNA was isolated from buccal cells and blood samples from cats in the multi-generational pedigree (Fig. 1) according to published procedures (Sambrook & Russell 2001; Oberbauer et al. 2003). Phenotypes were verified by visual inspection, breeder reports, segregation in families and photographs (Fig. 2). Relationship of the cats was verified by parentage testing with 19 microsatellites (data not shown). Pigmented cats that produced albino offspring were assumed to be obligate carriers of the complete albinism allele. Microsatellite FCA931, which is linked to TYR (Menotti-Raymond et al. 1999, 2003), was genotyped as previously described (Grahn et al. 2004), and the alleles were tested for concordant segregation with the colour phenotypes.

Tyrosinase exons were sequenced as previously described (Lyons et al. 2005) from three albino cats and three obligate carriers, as well as from three wild-type cats that were not associated with the albino pedigree. The TYR sequences of the albino cats and the wild-type cats were identical except for a cytosine deletion at position 975 in exon 2, which causes a frame shift and a premature stop codon in the protein translation nine codons downstream from the mutation. The deletion mutation in TYR and an allele of FCA931 segregated concordantly with the albino phenotype. Taken together, our results suggest that the TYR gene corresponds to the colour locus in cats and its alleles, from dominant to recessive, are as follows: C (full colour) > c\(^b\) (burmese) > c\(^b\) (siamese) > c (complete albino).

Keywords: albinism, cat, tyrosinase.

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which was confirmed by sequence and restriction fragment length polymorphism (RFLP) analyses (Lyons et al. 2005).

In our previous study (Lyons et al. 2005), mutations in TYR associated with the temperature-sensitive phenotypes of siamese and burmese cats were identified. Robinson (1991) suggested that an allele in TYR causes albinism because other species have the same phenotype associated with TYR mutations. Our analysis of an extended pedigree supports that the albinism phenotype is allelic to full colour (C), burmese (cb) and siamese (cs), suggesting the allelic series C > cb > cs based on mutations in TYR. However, sufficient breeding studies have not been performed to confirm the allelic series in cats, specifically, the interaction of full colour and burmese with the albino allele.

The putative albino mutation identified in this study would produce a truncated protein because a stop codon occurs in exon 2, nine amino acids downstream of the deletion. The amino acids located near the cytosine deletion are conserved among dogs, human, mice, cattle and rabbits (Fig. 3), further supporting that this mutation is a significant change in the protein. Expression studies and complementary DNA sequencing are needed to support this finding.

Albino cats have been reported in the literature (Todd 1951; Turner et al. 1981) but have not been well characterized. Blue-eyed vs. pink-eyed albino cats have not been clearly distinguished in the published reports (Bamber & Herdman 1931; Todd 1951; Leventhal 1982; Leventhal et al. 1985). Thus, it is unclear whether there is more than one non temperature-sensitive albinism allele in cats, as has been reported in mice (reviewed in Beermann et al. 2004), in humans (summarized at http://albinismdb.med.umn.edu/) and in cattle (Schmutz et al. 2004). The albino cats evaluated in this study have blue eyes. As with most blue-eyed cats, reduced pigment in the tapetum produces a reddish (as opposed to a 'greenish') tapetal reflection or 'eye-shine'. The c allele has been reserved for red-eyed (complete) albinism, but the difference in the tapetal reflex suggests that the single report of a red-eyed albino cat may be in error.

In conclusion, we propose that a cytosine deletion in TYR at position 975 in exon 2 is associated with albinism in cats. This mutation could be used in a DNA test to detect carriers.
and assist with breeding programmes. This finding also supports the use of the cat as a model for human **TYR**-associated albinisms.

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Figure 3 Exon 2 nucleotide and protein sequence alignments of feline and human *tyrosinase* (TYR). The TYR nucleotide sequences for *Felis catus* (FCA) and *Homo sapiens* (HSA) were AY743347 and M27160 respectively. The amino acids (aa’s) for each codon are listed below the nucleotide sequences. The albino mutation is a cytosine deletion at nucleotide 975 that causes a frameshift, leading to a stop (OCH) codon nine residues downstream of the deletion GenBank accession no. AY743347. The portion of the cat albino allele that is altered relative to the wild-type sequence is presented in bold. Amino acids that are conserved among dogs, human, mice and cattle are underlined. The rabbit has a single amino acid change in this region, replacing an alanine with a serine.