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Mapping of the Domestic Cat "*SILVER*" Coat Color Locus Identifies a Unique Genomic Location for Silver in Mammals

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Abstract

The *SILVER* locus has been mapped in the domestic cat, identifying a unique genomic location distinct from that of any known reported gene associated with silver or hypopigmentation in mammals. A demonstrated lack of linkage to *SILV*, the strong candidate gene for silver, led to the initiation of a genome scan utilizing 2 pedigrees segregating for silver coat color. Linkage mapping defined a genomic region for *SILVER* as a 3.3-Mb region, (95.87–99.21 Mb) on chromosome D2, (peak logarithm of the odds = 10.5, $\theta = 0$), which displays conserved synteny to a genomic interval between 118.58 and 121.85 Mb on chromosome 10 in the human genome. In the domestic cat, mutations at the *SILVER* locus suppress the development of pigment in the hair, but in contrast to other mammalian silver variants, there is an apparently greater influence on the production of pheomelanin than eumelanin pigment. The mapping of a novel locus for *SILVER* offers much promise in identifying a gene that may help elucidate aspects of pheomelanogenesis, a pathway that has been very elusive, and illustrates the promise of the cat genome project in increasing our understanding of basic biological processes of general relevance for mammals.

Key words: *coat color, domestic cat, genetic linkage mapping, pheomelanogenic, SILVER*

It is estimated that the cat was domesticated approximately 10 000 years ago (Vigne et al. 2004) in the Middle East (Driscoll et al. 2007), likely as a consequence of the development of the first villages and the storage of wild grain stocks which attracted an abundant source of rodents. This wild progenitor of the domestic cat, *Felis silvestris lybica*, the African wild cat, is difficult to distinguish today from a common domestic tabby cat with mackerel stripes set against a wild-type agouti coat background (Figure 1). Since domestication, a wide range of coat color and pattern variants have arisen in the domestic cat, which have not been reported in the wild cat, including a variety of coat colors, distinctive hair phenotypes, as well as coat patterns (stripes, spots, and blotches, including the unpatterned coat of the "ticked tabby"). This development of pelage polymorphism has been observed in most mammals which have experienced domestication, partly as a consequence of release from purifying selection in natural populations but also due to intense artificial selection in favor of color morphs or patterns that were pleasing to humans (Zeuner 1963; Trut 1999).

With the development of genomic resources in the domestic cat, including comprehensive genetic and radiation hybrid maps (Menotti-Raymond et al. 1999, 2003, 2009; Murphy et al. 2000, 2007; Davis et al. 2009; Schmidt-Küntzel et al. 2009), a 1.9× whole-genome sequence draft (Pontius et al. 2007), and an interactive web browser (Pontius and O'Brien 2007), several of the genes underlying this phenotypic variation have been mapped and/or characterized at a molecular genetic level, including black (Eizirik et al. 2003), brown, and cinnamon (Schmidt-Küntzel et al. 2005), dilute (Ishida et al. 2006), Siamese, and Burmese phenotypes, albino (Lyons et al. 2005; Imes et al. 2006), long hair (Drogemuller et al. 2007; Kehler et al. 2007), and orange (Schmidt-Küntzel et al. 2009).

The cat displays additional color morphs, which have not yet been mapped or characterized, including a silver pelage variant (Figure 1), which is due to the autosomal dominant

Figure 1. Images of a wild cat (right), *Felis silvestris lybica*, and the silver male Ocicat used in the generation of Pedigree Two.

action of what has been termed the "Inhibitor" locus (Vella et al. 1999). In the domestic cat, mutations at the Inhibitor or *SILVER* locus suppress the development of pigment in the hair, but in contrast to other mammalian silver variants, there is an apparently greater influence on the production of pheomelanin than eumelanin pigment (Vella et al. 1999). The characteristic "yellowish-orange" agouti band seen in wild-type cats, resulting from a shift in eumelanin to pheomelanin production (Eizirik et al. 2003), is nearly white or colorless in silver cats. Further, hairs in silver domestic cats display a silver (near colorless) base, with normal (including eumelanic, depending on other loci) pigmentation observed in the hair tips (Figure 2). A striking silver phenotype in the cat is "smoke," which stems from the effect of silver on a nonagouti (melanistic, i.e., black) background. The guard hairs in these cats display a silver base, with lengthened black tips, as compared with hairs in silver cats (Vella et al. 1999) (Figure 2). *SILVER* does not prevent the synthesis of pheomelanic pigments, as witnessed in orange, silver tabbies. However, the color of the orange pigmentation is somewhat different than observed in an orange, non-silver cat, being devoid of the warm brown tones seen in a classic orange cat (Pflueger S, personal communication).

A *SILVER* locus was first described in the mouse by Dunn and Thigpen (1930). Since then, genetic loci producing silver, or hypopigmentation phenotypes, have been reported in a number of organisms, including horses, dogs, cattle, mice, birds, chickens, and zebra fish (Martinez-Esparza et al. 1999; Kerje et al. 2004; Schonthaler et al. 2005; Brunberg et al. 2006; Clark et al. 2006; Kühn and Weikard 2007; Reissmann et al. 2007). The gene implicated in these "silver" phenotypes has been the *SILV* locus (also known as "silver homolog" or *PMEL17*), which generates a protein product important in early stages of melanosome biogenesis (Kobayashi et al. 1994; Zhou et al. 1994; Berson et al. 2001). The mode of inheritance is typically autosomal dominant. In zebra fish and dogs, defects in vision and hypopigmentation are associated with mutations at the *SILV* locus (Schonthaler et al. 2005; Clark et al. 2006). Dogs that carry the merle mutation, characterized as an insertion of a short interspersed element in *SILV*, exhibit patches of diluted pigment juxtaposed with patches of normal coloration and additionally suffer from

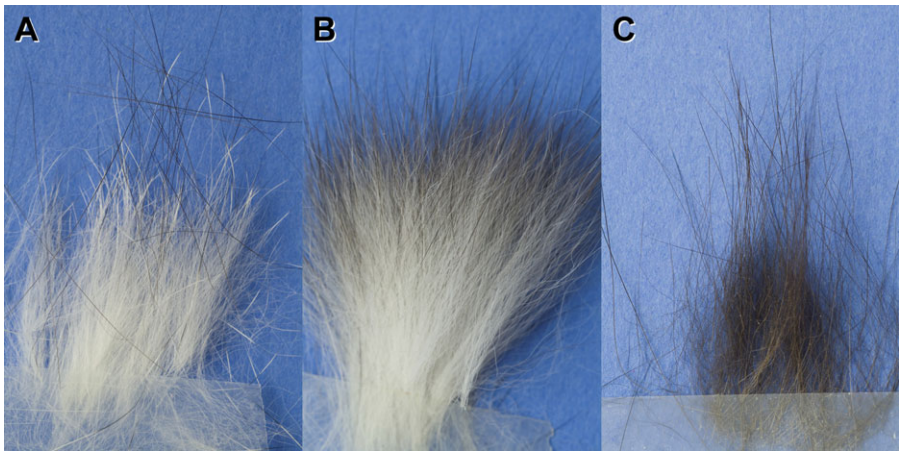

Figure 2. Panels demonstrate hairs from domestic cat silver (**A**), smoke (**B**), and melanistic (**C**) individuals.

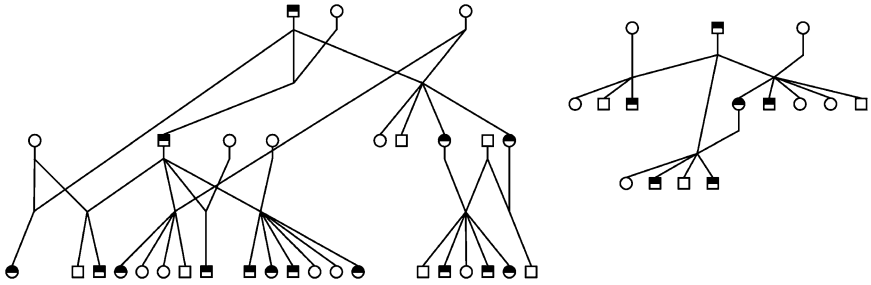

Figure 3. Pedigrees used for the mapping of the domestic cat *SILVER* locus; Pedigree One (left); Pedigree Two (right). Male, heterozygous for *SILVER*; female, heterozygous for *SILVER*.

auditory abnormalities (Clark et al. 2006). In humans, there are no reported mutations associated with the *SILV* gene, which is located on 12q13–q14. There are no reported pathologies associated with the silver phenotype in cats. Additional genes in mammals have been reported involved in hypopigmentation (Mariat et al. 2003; Cook et al. 2008). We report here the mapping of the *SILVER* locus in the domestic cat identifying a new locus for silver/hypopigmentation in mammals.

Materials and Methods

Animals

Two pedigrees were utilized (Figure 3). Pedigree One was developed at the National Institutes of Health Animal Center (NIHAC). The pedigree was founded with a purebred, silver male cat of the Egyptian Mau breed, which was crossed with 3 unrelated non-silver outbred (they did not belong to a registered breed) females. Seven progeny were produced, 5 of which were silver, demonstrating that the parental male was heterozygous for *SILVER*. These 5 F_1 individuals (4 females and a male) were backcrossed to non-silver outbred cats, producing a third-generation of 23 animals, 19 of which could be confidently phenotyped for the *SILVER* locus. Overall, the F_1 and backcross individuals exhibited an approximate 1:1 ratio of silver ($n = 14$) to non-silver ($n = 12$) phenotypes. Another pedigree (referred to as "Pedigree Two" henceforth) that segregated for silver was provided by a cooperating cat breeder. One silver male, a purebred Ocicat, was mated to 2 females producing 12 progeny, 5 of which were silver and 7 non-silver.

DNA Extraction

For all individuals from Pedigree One, blood samples were collected as a standard source of DNA; in addition, skin biopsies were collected from each animal according to NIHAC animal protocols and cell lines were established as a source of high-quality genomic material. Buccal swab samples were supplied for individuals in Pedigree Two. DNA was extracted from whole blood and fibroblast cell lines using a QIAamp DNA blood Midi or Mini Kit (Qiagen) for blood or buccal samples, respectively, using manufacturer's protocols. DNA was quantified using a Hoefer DNA Quant 200 Flurometer (Amersham Biosciences). A proportion of each sample was diluted to a standard concentration of 2.5 ng/μl with sterile distilled water (Quality Biological).

Polymerase chain reaction Amplification and Genotyping of Microsatellites

A genome scan was initiated using microsatellites selected at regular intervals along the cat genome (Murphy et al. 2007; Menotti-Raymond et al. 2009). Polymerase chain reaction (PCR) amplification of microsatellites was performed with a touchdown PCR protocol as described previously (Menotti-Raymond et al. 2005). Sample electrophoresis and genotyping, as well as Mendelian inheritance checking, were carried out as previously described (Ishida et al. 2006).

Development of Additional Microsatellites for Fine Mapping of *SILVER*

After linkage with *SILVER* was established to a genomic region using previously published cat microsatellites, additional markers from this candidate segment region were mined from the cat 1.9× whole-genome sequence (Pontius et al. 2007). Microsatellite markers, selected based on their location on cat chromosome D2, were mined from the GARFIELD cat genome browser (http://lgd.abcc.ncifcrf.gov/cgi-bin/gbrowse/cat/) (Pontius and O'Brien 2007). These include all loci for *SILVER* mapping in Table 1 with prefix "D2_." Primers for new loci (Supplementary material, Appendix 1) were designed with Primer 3 (http://frodo.wi.mit.edu/cgi-bin/primer3/primer3_www.cgi) (Rozen and Skaletsky 2000), including an M13 tail for fluorescent labeling of PCR products (Boutin-Ganache et al. 2001).

Genetic Linkage Mapping

Single-marker logarithm of the odds (LOD) scores were computed, using Superlink (Fishelson and Geiger 2002, 2004), as described in Ishida et al. (2006) and Kehler et al. (2007). Since the 2 pedigrees were established each from a single male, one a purebred Egyptian Mau and the other a purebred Ocicat, we analyzed the data both as a single pedigree and as 2 independent pedigrees. *SILVER* mapped to the same genomic region in both pedigrees (data not shown).

Table 1. Microsatellite markers utilized in mapping of *SILVER*

Marker[a]	LOD	Q	Cat Chr D2	Dog Chr 28[b]	Human Chr 10[c]
FCA955	2.8	0.2	86,022,426	21,788,479	108,516,870
FCA1239	2.0	0.1	86,789,157	22,486,644	109,388,134
FCA1241	3.7	0.2	91,583,985	26,143,901	113,744,643
D2_93.3	3.4	0.05	93,358,579	28,191,399	116,105,982
D2_93.9	5.9	0.1	93,900,284	28,668,678	116,660,785
D2_94.5	6.2	0.1	94,524,844	29,257,166	117,375,668
D2_95.1	6.8	0.05	95,192,200	29,813,138	117,921,715
FCA954	5.8	0.05	95,823,888	30,338,383	118,536,757
FCA1240	7.4	0.05	95,875,325	30,384,390	118,588,972
D2_96.1	10.5	0	96,114,956	30,595,675	118,846,522
D2_96.9	8.1	0	96,990,099	31,332,116	119,656,273
D2_98.1	10.2	0	98,100,274	32,256,893	120,742,485
D2_98.6	7.8	0	98,601,083	32,659,233	121,227,619
D2_99.16	5.3	0	99,167,851	33,131,599	121,797,461
D2_99.21	6.7	0.05	99,219,025	33,175,512	121,850,894
D2_99.27	6.7	0.05	99,275,747	33,215,309	121,887,548
F41	5.1	0.1	99,706,534	33,563,419	122,318,976
FCA1242	1.9	0.1	105,677,501	38,419,330	127,982,490
FCA1243	0.6	0.3	107,394,183	39,793,387	129,659,013

[a] Markers in bold are previously published; other markers were mined from GARFIELD genome browser as described in the Materials and methods.

[b] Estimated by Blat genome search of 400 bp of cat genomic DNA flanking sequence to Dog May 2005 assembly using the UCSC genome browser.

[c] Dog coordinates converted to the position on Human March 2006 assembly using the UCSC genome browser.

Results and Discussion

We began our analysis by genotyping a microsatellite marker (FCA867, at 102.1 Mb on B4) closely linked to the strong candidate locus for *SILVER*, the *SILV* gene on cat chromosome B4, 96.37–96.39 Mb (Murphy et al. 2007). A demonstrated lack of linkage between FCA867 and *SILVER* (LOD = −5.7, $\theta = 0$), with a LOD score below the frequently used exclusion criterion of −2 (Ott 1991), led to the initiation of a genome scan using microsatellites selected at regular intervals along the cat genome (Murphy et al. 2007; Menotti-Raymond et al. 2009). Ninety-six microsatellites were genotyped in the 2 pedigrees before significant linkage was detected with microsatellite FCA955 (LOD = 2.79, $\theta = 0.2$) on cat chromosome D2. Fine-scale mapping was performed utilizing 7 previously published microsatellite markers in the vicinity of FCA955 and 11 additional microsatellite markers selected from the interactive cat genome browser GARFIELD (http://lgd.abcc.ncifcrf.gov/cgi-bin/gbrowse/cat) (Pontius and O'Brien 2007) (Supplementary material, Appendix 1). A candidate region for *SILVER* was defined as a 3.3-Mb region, between markers FCA1240 (95.87 Mb) and D2_99.21 (99.21 Mb) on chromosome D2 (peak LOD = 10.5, $\theta = 0$) (Table 1), which displays conserved synteny to a genomic interval between 118.58 and 121.85 Mb on chromosome 10 in the human genome. According to the human genome (build 36), (http://www.ncbi.nlm.nih.gov/projects/mapview/stats/BuildStats.cgi?taxid=9606&build=36&ver=3), this region includes approximately 17 genes (Supplementary material, Appendix 2), none that have been previously associated in other species with silver, dilute, or hypopigmentation.

An attractive candidate gene in the feline *SILVER* interval is *SLC18A2*, a member of the solute carrier family 18. *SLC18A2* has been described in humans and rodent models as a vesicular monoamine transporter that accumulates cytosolic monoamines into vesicles (Peter et al. 1995). Mutations in related genes (*SLC45A* and *SLC36A1*) are responsible for cream and champagne coat color hypopigmentation in horses (Mariat et al. 2003; Cook et al. 2008), hypopigmentation in the mouse underwhite (uw) phenotype (Lehman et al. 2000), and pale skin in European populations (Lamason et al. 2005). Analysis of the feline *SLC18A2* is currently in progress.

We have thus mapped the *SILVER* locus in the domestic cat, identifying a new genomic location for silver or hypopigmentation in mammals. The absence of the pheomelanic agouti band in silver cats and the unique quality of orange pigmentation in an orange, silver cat additionally suggests that *SILVER* in the domestic cat may possibly play a role in the elusive pheomelanic pathway—either in regulation of synthesis of pheomelanin or in the structure or molecular composition of the pheomelanic pigment.

Little is known about the regulation of the pheomelanic pathway or about the structure, molecular composition, and photobiology of pheomelanin (Simon 2003). The mapping of a novel locus for *SILVER* to a relatively short interval offers much promise in identifying a gene that may help elucidate aspects of the pheomelanic pathway and illustrates the promise of the cat genome project in increasing our understanding of basic biological processes of general relevance for mammals.

Supplementary Material

Supplementary material can be found at http://www.jhered.oxfordjournals.org/.

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