Incorporating Mouse Genome
Mammalian Genome
Genes and Phenotypes

Association of an Agouti allele with fawn or sable coat color in domestic dogs

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Abstract

The type of pigment synthesized in mammalian hair, yellow–red pheomelanin or black–brown eumelanin, depends on the interaction between Agouti protein and the Melanocortin 1 receptor. Although the genetics of pigmentation is broadly conserved across most mammalian species, pigment type-switching in domestic dogs is unusual because a yellow–tan coat with variable amounts of dark hair is thought to be caused by an allele of the *Agouti* locus referred to as *fawn* or *sable* (a^y). In a large survey covering thirty seven breeds, we identified an *Agouti* allele with two missense alterations, A82S and R83H, which was present (heterozygous or homozygous) in 41 dogs (22 breeds) with a fawn or sable coat, but was absent from 16 dogs (8 breeds) with a black-and-tan or tricolor phenotype. In an additional 33 dogs (14 breeds) with a eumelanic coat, 8 (German Shepherd Dogs, Groenendaels, Schipperkes, or Shetland Sheepdogs) were homozygous for a previously reported mutation, *non-agouti* R96C; the remainder are likely to have carried dominant black, which is independent of and epistatic to *Agouti*. This work resolves some of the complexity in dog coat color genetics and provides diagnostic opportunities and practical guidelines for breeders.

Introduction

Shades and patterns of coat color are a remarkably diverse trait among domestic dogs, with certain breeds exhibiting a specific phenotype, and other breeds exhibiting one of several phenotypes. For example, Rhodesian Ridgebacks typically occur in various shades of yellow–tan, usually referred to as fawn. By contrast, a phenotype shared across several breeds, including the Doberman Pinscher, the Rottweiler, some Dachshunds, and many Spaniels, is the black-and-tan pattern, in which a black background is marked by discrete and regular areas of reddish yellow around the ears, supraorbital region, lower face, chest, inner aspects of the proximal limbs, and dorsal aspects of the distal limbs. All of these phenotypes are thought to be controlled by variation of the *Agouti* gene.

Agouti encodes a paracrine signaling molecule which causes hair follicle melanocytes to synthesize reddish yellow pheomelanin instead of black or brown eumelanin, so-called pigment type-switching (Bultman et al. 1992; Miller et al. 1993; reviewed in Barsh et al. 2000). In laboratory mice, variation in pigment type-switching is brought about via two sets of *Agouti* mRNA isoforms that differ by virtue of their untranslated first exons and associated promoter activity (Vrieling et al. 1994; Chen et al. 1996). ''Ventral-specific'' isoforms are expressed throughout the anagen phase of hair growth, but only in ventral skin, and are responsible for the characteristic pale yellow appearance of ventral hairs. By contrast, ''hair cycle-specific'' isoforms are expressed throughout the body but only for a brief period during early anagen, such that individual hairs have a subapical band of yellow pigment on a black background. Both isoforms are expressed in the mouse *white-bellied Agouti* (A^W) allele, which causes banded hairs on the dorsum together with pale yellow hairs on the ventrum. Agouti protein is an inhibitory ligand for the Melanocortin 1 receptor (Mc1r), a seven-transmembrane protein expressed on melanocytes whose activation leads to increased production of cAMP (Lu et al. 1994; Ollmann et al. 1998). In

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