

BRIEF REPORT

Golden cats: A never-ending story!

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Abstract

In the British feline breed a golden coat modification, called light-gold, akita or copper, was reported by breeders during the 2010s. This modification restricted eumelanin to the tip of the tail and hairs showed a wideband modification. Pedigree analyses revealed an autosomal recessive inheritance pattern. A single candidate region was identified using a genome-wide association study. Within that region, we identified *CORIN* (Corin, serine peptidase) as the strongest candidate gene, since two *CORIN* variants have previously been identified in Siberian cats with a golden phenotype. A homozygous *CORIN*:c.2425C>T nonsense variant was identified in copper British cats. Segregation of the variant was consistent with recessive inheritance. This nonsense *CORIN*:c.2425C>T variant, located in *CORIN* exon 19, was predicted to produce a truncated *CORIN* protein – *CORIN*:p.(Arg809Ter) – that would lack part of the scavenger receptor domain and the trypsin-like serine protease catalytic domain. All 30 copper cats were *T/T* homozygous for the variant, which was also found in 20 *C/T* heterozygous British control cats but was absent in 340 cats from the 99 Lives dataset. Finally, genotyping of 218 cats from 12 breeds failed to identify carriers in cats from other breeds. We propose that this third *CORIN*:c.2425C>T variant represents the *wb^{B^{SH}}* (*British recessive wideband*) allele in the domestic cat.

KEYWORDS

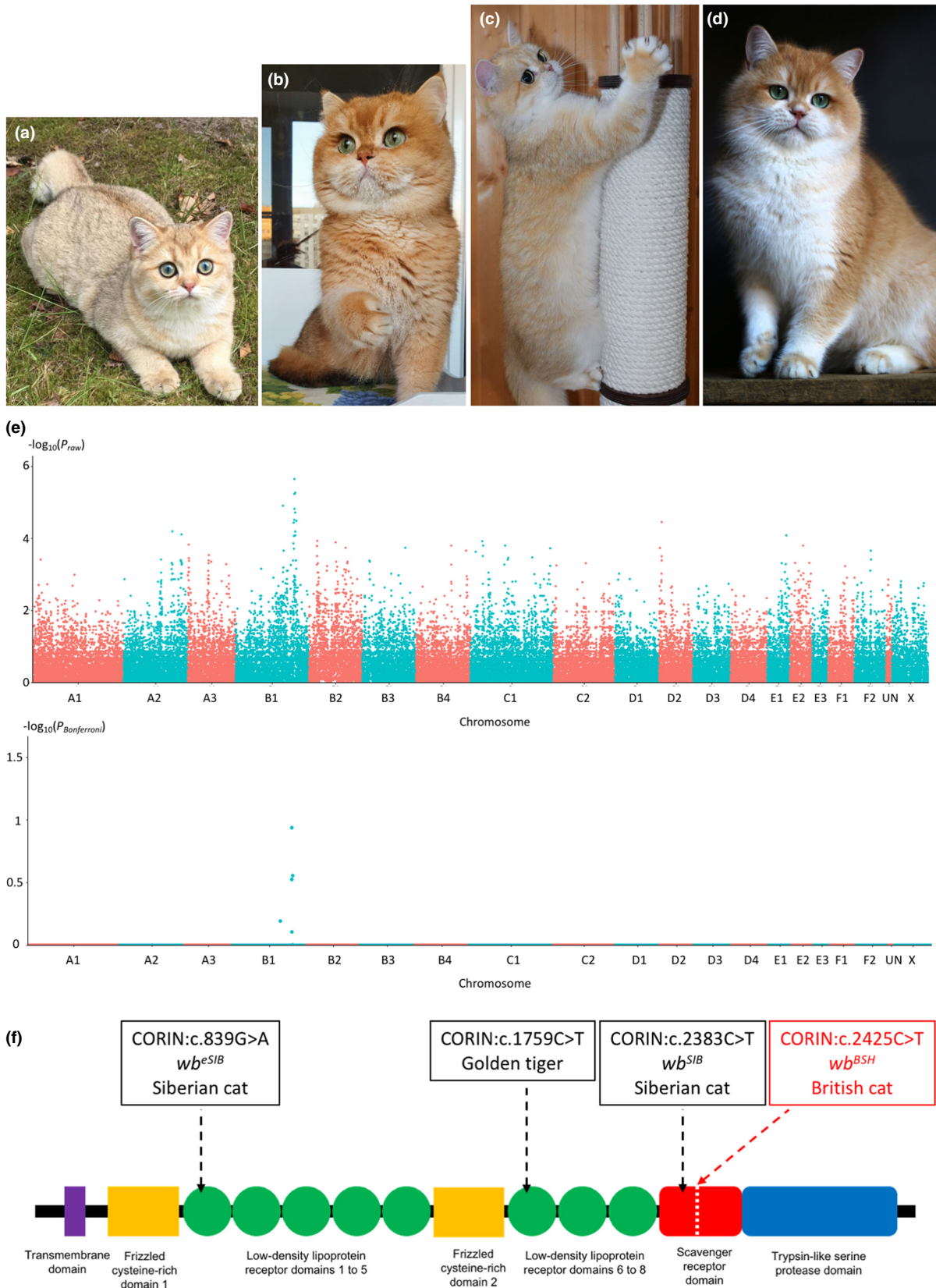
agouti, ASIP, coat, *CORIN*, *Felis catus*, golden, hair, shaded, sunshine, ticked, wideband

In the Siberian cat breed, two variants were identified in the *CORIN* (Corin, serine peptidase) gene, a suppressor of the ASIP (agouti signaling protein) pathway (Enshell-Seijffers et al., 2008) that causes golden coat modifications characterized by enlarged subapical pheomelanin bands in hairs and reduced dark tips (Abitbol et al., 2022; Beauvois et al., 2021). These modifications, called sunshine and extreme-sunshine, are similar to the golden modification of tigers (Xu et al., 2017). In British cats, breeders from Germany and Russia have reported

since the 2010s a coat modification that is distinct from the known golden shaded (Vella et al., 1999) and golden ticked phenotypes (Lyons et al., 2021). This modification was supposed to be polygenic as several phenotypes differing in their warm tone and countershading were observed, ranging from a classical golden ticked phenotype to a ‘copper’ phenotype characterized by a red mantle with marked ivory belly and ivory spots on the upper-sides of the paws (Figure 1a–d). However, careful examination of pedigree data indicated a probable autosomal

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recessive inheritance pattern. DNA and phenotypic data from these copper British cats and from control cats were collected. Twenty-five British cats (including 10

copper cats) were genotyped using the Illumina Feline 63 k SNP array, among which 60 599 SNPs yielded usable results (minor allele frequency >5%, genotyping

FIGURE 1 The copper phenotype in British cats is governed by a *CORIN* nonsense allele. (a) Golden ticked phenotype in a black tabby British cat. Note the blond tone and the agouti phenotype owing to agouti banded hairs. (b–d) Copper phenotype variations in black tabby British cats. (b) Note the red tone with a discrete lightening of the belly, ivory marks on the uppersides of the paws and the black tail tip. (c) Note the blond to apricot tone with marked ivory belly and ivory marks on the uppersides of the paws. (d) Note the red mantle with marked light ivory to white belly and large ivory marks on the uppersides of the paws. The three copper cats (b–d) were *T/T* homozygous for the *CORIN*:C.2425C>T variant and showed tipped hairs. The golden ticked cat (a) showed agouti ticked hairs and was heterozygous for the *CORIN*:C.2425C>T variant (Table S3, Figure S2). (e) Manhattan plot of the genome-wide association study. The plots represent the P_{raw} and $P_{\text{Bonferroni}}$ values of each SNP included in the case–control association study. The association study compared the 10 copper British cats with 15 control British cats. A suggestive association with chromosome B1 was detected. The three SNPs with the highest association were chrB1.188265817, chrB1.188367525 and chrB1.188505613, with a P_{raw} value of 2.21×10^{-6} and a $P_{\text{Bonferroni}}$ value of 0.11 (Table S1). UN, Unknown. (f) Schematic of the 13 domains of *CORIN* (Appendix S1). The *CORIN*:C.839G>A missense variant of extreme-sunshine Siberian cats, the *CORIN*:C.1759C>T missense variant of golden tigers and the *CORIN*:C.2383C>T missense variant of sunshine Siberian cats are depicted in black. The *CORIN*:C.2425C>T nonsense variant of copper British cats is depicted in red

rate >95%). All 25 cats had genotyping rates >95% and all were conserved for the analysis. Following basic case–control analysis, the genomic inflation factor was 1.59 and the 25 highest significant associations were identified for 25 SNPs, among which 18 markers were located on chromosome B1 (Appendix S1, Figure 1e, Table S1). After Bonferroni correction of the P_{raw} values for multiple tests, no SNP had a significant $P_{\text{Bonferroni}}$ value (Figure 1e, Table S1). Seventeen of the 18 SNPs from chromosome B1 were located between position 164 738 782 bp and position 175 627 824 bp (Table S1) according to *Felis_catus* 9.0 reference genome and defined the genome-wide association study candidate region. This region contains a strong candidate gene, *CORIN* (chromosome B1: 167 578 182 bp to 167 835 768 bp, *Felis_catus* 9.0). Exons and exon–intron boundaries from *CORIN* were sequenced in two copper cats and compared with the reference feline sequence (Appendix S1, Table S2). Three variants were identified. We found the previously described *CORIN*:c.1449C>G SNP (rs43981625, ensembl.org; Beauvois et al., 2021) predicted by PROVEAN to be a neutral variant (Appendix S1) and a synonymous *CORIN*:c.2684C>T variant. In exon 19, we found that the two copper cats were *T/T* homozygous for a *CORIN*:c.2425C>T nonsense variant predicted to change an arginine at position 809 in the protein into a stop codon: *CORIN*:p.(Arg809Ter).

We genotyped a total of 84 British cats for the *CORIN*:c.2425C>T variant. All 30 copper cats were *T/T* homozygous. The copper cat group included cats with or without a marked ivory belly but showing a gold to red tone and ivory marks on the uppersides of the paws (Figure 1b–d). Among 54 British control cats, 20 were *C/T* heterozygous for the *CORIN*:c.2425C>T variant and included five copper obligate carriers. Additionally, in the group of 17 golden ticked and golden shaded British control cats, 13 individuals were *C/T* heterozygous and four cats were wild-type homozygous (Table S3).

We searched for the *CORIN*:c.2425C>T variant in the 340 cats of the 99 Lives cat whole genome sequencing project (Buckley et al., 2020) and we genotyped a total of 218 control cats from 12 breeds for *CORIN*:c.2425C>T, including golden shaded Persian and Exotic cats and

sunshine Siberian cats. We failed to identify the mutant allele (Table S3).

Alignment of the feline *CORIN* protein sequence with the human sequence and the sequences from 12 mammals with agouti hairs (Figure S1, Table S4) shows that the *CORIN*:c.2425C>T nonsense variant was predicted to produce a truncated *CORIN* protein – *CORIN*:p.(Arg809Ter) – lacking part of the scavenger receptor domain and the trypsin-like serine protease catalytic domain. *CORIN* was described as a transmembrane serine protease functioning as a suppressor of the agouti pathway. It regulates the length of the functioning period of ASIP during the hair growth cycle, producing tipped hairs characterized by enlarged subapical pheomelanin bands and reduced dark tips (Enshell-Seijffers et al., 2008; Xu et al., 2017). In copper cats we observed only tipped hairs whereas golden ticked cats showed non-modified agouti hairs (Figure S2). Thus, the copper modification of British cats was fully consistent with a wideband phenotype.

In conclusion, we identified a third *CORIN* variant associated with the copper modification of British cats. We propose that this *CORIN*:c.2425C>T variant represents the *wb^{B^{SH}}* (*British recessive wideband*) allele in the domestic cat, which further enlarges the panel of recessive *CORIN* wideband alleles described in animals.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

SNP genotyping data were deposited at OSF (https://osf.io/xe9rn/?view_only=3c8858b9ff1c4a0c86e2e6681bcaa2ad).

Genomic sequences of *CORIN* exon 19 from wild-type and copper cats (*Felis catus*) were submitted to GenBank. Accession numbers are GenBank ID: MW288825 for the wild-type allele and GenBank ID: ON640807 for the *CORIN*:c.[2425C>T] variant allele. Sequences for the cat analysis of the 99 Lives project (Buckley et al., 2020) are available under BioProject accession IDs PRJNA308208 and PRJNA288177 at the sequence read archive (<https://www.ncbi.nlm.nih.gov/sra>).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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