Title

A TYR-iffic discovery: Identification of a second TYR variant associated with acromelanism in dogs

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BRIEF REPORT

A TYR-iffic discovery: Identification of a second *TYR* variant associated with acromelanism in dogs

Acromelanism is a form of albinism that results from pigmentation being affected by temperature and causes a 'Himalayan' or 'colorpoint' coat pattern in affected animals. Tyrosinase, encoded by the *TYR* gene, is an enzyme that is essential for the biosynthesis of melanin (Slominski, 2002). The Himalayan coat color, where the extremities are darker and the torso remains lighter, is due to mutations that result in a temperature-sensitive tyrosinase protein that causes melanin synthesis to occur only in cooler areas of the body. Mutations associated with the Himalayan-type phenotype have been identified in multiple species, including cats (Lyons et al., 2005; Schmidt-Küntzel et al., 2005; Yu et al., 2019), rabbits (Aigner et al., 2000), mice (Beermann et al., 2004; Kwon et al., 1989), mink (Benkel et al., 2009), dogs (Bychkova et al., 2021), baboons (Koga et al., 2020), syrian hamsters (Sakamoto & Hirobe, 2023) and domesticated canaries (Guimarães-Moreira et al., 2024). Some mutations in *TYR* have been identified as resulting in complete albinism (Imes et al., 2006; Yan et al., 2019). In humans, mutations in this gene that impact pigmentation are classified as Type 1 oculocutaneous albinism (Spritz et al., 1997). Oculocutaneous albinism is a group of inherited disorders characterized by reduced melanin in the skin, hair and eyes. Six of the identified types described in humans are linked to mutations in distinct genes (Yang et al., 2019): *TYR* (OCA1), *OCA2* (OCA2), *TYRP1* (OCA3), *SLC45A2* (OCA4), *SLC24A5* (OCA6) and *LRMDA* (OCA7). In dogs, mutations affecting pigmentation phenotype have been associated with four of those genes, comprising *TYR* (Bychkova et al., 2021), *OCA2* (Caduff et al., 2017b), *TYRP1* (Hrckova Turnova et al., 2017; Schmutz et al., 2002; Van Buren et al., 2021; Wright et al., 2019) and *SLC45A2* (Caduff et al., 2017a; Winkler et al., 2014; Wijesena & Schmutz, 2015). Here, we investigated a family of rescue dogs that display a characteristic Himalayan coat color and report a second *TYR* variant associated with this phenotype in canids.

Buccal samples were collected from one non-Himalayan and five Himalayan dogs, with written consent obtained from all owners to participate in the research. These six individuals (CP1, CP2, CP3, CP4, CP5 and CP6) were from two litters (three from each) surrendered to the same shelter approximately 6 months apart with the information that they have the same parents who do not have a Himalayan coat color. The entire *TYR* coding sequence was sequenced in CP1 and then only exon 1 was subsequently sequenced in the other five individuals, using previously described primer sequences (Bychkova et al., 2021). Genotyping was performed with Sanger sequencing at the UC Berkeley Sanger Sequencing Facility and was visualized with SEQUENCHER 5.4.6 software.

We identified a novel *TYR* variant (c.229C>T, p.Arg77Trp) in exon 1 in the homozygous state in the five Himalayan dogs. This variant was predicted to be deleterious to protein function by the PredictSNP consensus classifier with 87% confidence and has been named the 'c^{h2}' variant. All five Himalayan dogs were c^{h2}/c^{h2} and the one non-Himalayan dog was homozygous wild type, as shown in Figure 1. Interestingly, the c^{h2} variant is in the same codon as the first identified Himalayan variant in dogs (c.230G>A, p.Arg77Gln) (Bychkova et al., 2021).

A commercial coat color test was conducted through the UC Davis Veterinary Genetics Laboratory to evaluate the background coat color of the individuals. The genetic results are presented in Table S1.

To assess kinship between the six individuals and confirm suspected relatedness, a short tandem repeat panel was performed by the UC Davis Veterinary Genetics Laboratory. A matrix was constructed between each pair of individuals using 53 autosomal short tandem repeats, and the proportion of shared alleles was assessed, similar to previous reports (Sosiawan et al., 2019; Yudianto et al., 2022). Based on Mendelian inheritance and assuming non-linkage, full siblings are expected to exhibit 25% two-allele sharing, 50% one-allele sharing and 25% no-allele sharing (Moffatt et al., 1994). In this analysis, each potential pair exhibited 9.4–26.4% two-allele sharing, 64.2–90.6% one-allele sharing and 0–13.2% no allele sharing (Table S2), suggesting some deviation from the 25–50–25% expectation but still indicating a degree of relatedness. The increased allele sharing observed may also indicate inbreeding effects, which can shift allele sharing ratios away from Mendelian predictions (Kamarudin et al., 2020).

We suspect the c^{h2} variant to be *de novo* to this family line, as it was not identified in any of the 668

FIGURE 1 The six dogs genotyped in this study: (a) individual CP1; (b) CP1 and individuals born from the second litter; (c) CP1 – after the coat was clipped, it grew back darker; (d) CP2; (e) CP3 as a puppy; (f) CP4 as a puppy; (g) CP5; and (h) CP6, which is wild type.

domestic dogs and 54 wild canids present in the The Dog Biomedical Variant Database Consortium (Plassais et al., 2019). Given that both parents are presumed to be wild type, we predict this variant to be recessive, similar to other Himalayan mutations in other species as well as in the previously identified dog mutation affecting the same codon (Bychkova et al., 2021).

AUTHOR CONTRIBUTIONS

Samantha L. Van Buren: Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; software; formal analysis; data curation. **Anushka Panjwani:** Validation; writing – review and editing. **Carrie J. Finno:** Writing – review and editing; investigation; project administration; supervision; resources.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All relevant data are available in the manuscript text and supporting information.

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REFERENCES

Aigner, B., Besenfelder, U., Müller, M. & Brem, G. (2000) Tyrosinase gene variants in different rabbit strains. *Mammalian Genome*, 11(8), 700–702. Available from: https://doi.org/10.1007/s003350010120

Beermann, F., Orlow, S.J. & Lamoreux, M.L. (2004) The Tyr (albino) locus of the laboratory mouse. *Mammalian Genome*, 15(10), 749–758. Available from: https://doi.org/10.1007/s00335-004-4002-8

Benkel, B.F., Rouvinen-Watt, K., Farid, H. & Anistoroaei, R. (2009) Molecular characterization of the Himalayan mink. *Mammalian Genome*, 20(4), 256–259. Available from: https://doi.org/10.1007/s00335-009-9177-6

Bychkova, E., Viktorovskaya, O., Filippova, E., Eliseeva, Z., Barabanova, L., Sotskaya, M. et al. (2021) Identification of a candidate genetic variant for the Himalayan color pattern in dogs. *Gene*, 769, 145212. Available from: https://doi.org/10.1016/j.gene.2020.145212

Caduff, M., Bauer, A., Jagannathan, V. & Leeb, T. (2017a) A single base deletion in the SLC45A2 gene in a bullmastiff with oculocutaneous albinism. *Animal Genetics*, 48(5), 619–621. Available from: https://doi.org/10.1111/age.12582

Caduff, M., Bauer, A., Jagannathan, V. & Leeb, T. (2017b) OCA2 splice site variant in German Spitz dogs with oculocutaneous albinism. *PLoS One*, 12(10), e0185944. Available from: https://doi.org/10.1371/journal.pone.0185944

Guimarães-Moreira, M., Marques, C.I., Afonso, S., Lacerda, B., Carneiro, M. & Araújo, P.M. (2024) A missense mutation in the tyrosinase gene explains acromelanism in domesticated canaries. *Animal Genetics*, 55, 838–842. Available from: https://doi.org/10.1111/age.13481

Hrckova Turnova, E., Majchrakova, Z., Bielikova, M., Soltys, K., Turna, J. & Dudas, A. (2017) A novel mutation in the TYRP1 gene associated with brown coat colour in the Australian shepherd dog breed. *Animal Genetics*, 48(5), 626. Available from: https://doi.org/10.1111/age.12563

Imes, D.L., Geary, L.A., Grahn, R.A. & Lyons, L.A. (2006) Albinism in the domestic cat (*Felis catus*) is associated with a tyrosinase (TYR) mutation. *Animal Genetics*, 37(2), 175–178. Available from: https://doi.org/10.1111/j.1365-2052.2005.01409.x

Kamarudin, N.J., Wang, V.C., Tan, X.T., Ramesh, A. & Ling, M.H. (2020) A simulation study on the effects of founding population size and number of alleles per locus on the observed population genetic profile: implications to broodstock management. *EC Veterinary Science*, 5, 176–180.

Koga, A., Hisakawa, C. & Yoshizawa, M. (2020) Baboon bearing resemblance in pigmentation pattern to Siamese cat carries a missense mutation in the tyrosinase gene. *Genome*, 63(5), 275–279. Available from: https://doi.org/10.1139/gen-2020-0003

Kwon, B.S., Halaban, R. & Chintamaneni, C. (1989) Molecular basis of mouse Himalayan mutation. *Biochemical and Biophysical Research Communications*, 161(1), 252–260. Available from: https://doi.org/10.1016/0006-291x(89)91588-x

Lyons, L.A., Imes, D.L., Rah, H.C. & Grahn, R.A. (2005) Tyrosinase mutations associated with Siamese and Burmese patterns in the domestic cat (*Felis catus*). *Animal Genetics*, 36(2), 119–126. Available from: https://doi.org/10.1111/j.1365-2052.2005.01253.x

Moffatt, M.F., Hill, M.R., Cornélis, F. et al. (1994) Genetic linkage of T-cell receptor alpha/delta complex to specific IgE responses. *Lancet*, 343(8913), 1597–1600. Available from: https://doi.org/10.1016/s0140-6736(94)93057-0

Plassais, J., Kim, J., Davis, B.W., Karyadi, D.M., Hogan, A.N., Harris, A.C. et al. (2019) Whole genome sequencing of canids reveals genomic regions under selection and variants influencing morphology. *Nature Communications*, 10(1), 1489. Available from: https://doi.org/10.1038/s41467-019-09373-w

Sakamoto, A. & Hirobe, T. (2023) Isolation of a new line of Syrian hamster having a novel p.Leu262Pro mutation of tyrosinase with progressive pigmentation in its eyes and ears. *Journal of Dermatological Science*, 110(2), 72–75. Available from: https://doi.org/10.1016/j.jdermsci.2023.04.005

Schmidt-Küntzel, A., Eizirik, E., O'Brien, S.J. & Menotti-Raymond, M. (2005) Tyrosinase and tyrosinase related protein 1 alleles specify domestic cat coat color phenotypes of the albino and brown loci. *The Journal of Heredity*, 96(4), 289–301. Available from: https://doi.org/10.1093/jhered/esi066

Schmutz, S.M., Berryere, T.G. & Goldfinch, A.D. (2002) TYRP1 and MC1R genotypes and their effects on coat color in dogs. *Mammalian Genome*, 13(7), 380–387. Available from: https://doi.org/10.1007/s00335-001-2147-2

Slominski, A. (2002) Coming of age of melanogenesis-related proteins. *Archives of Pathology & Laboratory Medicine*, 126(7), 775–777. Available from: https://doi.org/10.5858/2002-126-0775-COAOMR

Sosiawan, A., Yudianto, A., Furqoni, A.H., Nzilibili, S.M.M. & Nuraini, I. (2019) Full-sibling allelic frequency and sharing among Madurese: STR technique by 12 locus and the sex-typing amelogenin gene. *Egyptian Journal of Forensic Sciences*, 9, 38. Available from: https://doi.org/10.1186/s41935-019-0143-5

Spritz, R.A., Oh, J., Fukai, K., Holmes, S.A., Ho, L., Chitayat, D. et al. (1997) Novel mutations of the tyrosinase (TYR) gene in type I oculocutaneous albinism (OCA1). *Human Mutation*, 10(2), 171–174. Available from: https://doi.org/10.1002/(SICI)1098-1004(1997)10:2<171::AID-HUMU11>3.0.CO;2-X

Van Buren, S.L., Mickelson, J.R. & Minor, K.M. (2021) A novel TYRP1 mutation associated with brown coat color in Siberian huskies. *Animal Genetics*, 52(2), 245–246. Available from: https://doi.org/10.1111/age.13037

Wijesena, H.R. & Schmutz, S.M. (2015) A missense mutation in SLC45A2 is associated with albinism in several small long haired dog breeds. *The Journal of Heredity*, 106(3), 285–288. Available from: https://doi.org/10.1093/jhered/esv008

Winkler, P.A., Gornik, K.R., Ramsey, D.T., Dubielzig, R.R., Venta, P.J., Petersen-Jones, S.M. et al. (2014) A partial gene deletion of SLC45A2 causes oculocutaneous albinism in Doberman pinscher dogs. *PLoS One*, 9(3), e92127. Available from: https://doi.org/10.1371/journal.pone.0092127

Wright, H.E., Schofield, E., Mellersh, C.S. & Burmeister, L.M. (2019) A novel TYRP1 variant is associated with liver and tan coat colour in Lancashire heelers. *Animal Genetics*, 50(6), 783. Available from: https://doi.org/10.1111/age.12839

Yan, S., Zhao, D., Hu, M., Tan, X., Lai, W., Kang, J. et al. (2019) A single base insertion in the tyrosinase gene is associated with albino phenotype in silver foxes (*Vulpes vulpes*). *Animal Genetics*, 50(5), 550. Available from: https://doi.org/10.1111/age.12816

Yang, Q., Yi, S., Li, M., Xie, B., Luo, J., Wang, J. et al. (2019) Genetic analyses of oculocutaneous albinism types 1 and 2 with four novel mutations. *BMC Medical Genetics*, 20(1), 106. Available from: https://doi.org/10.1186/s12881-019-0842-7

Yu, Y., Grahn, R.A. & Lyons, L.A. (2019) Mocha tyrosinase variant: a new flavour of cat coat coloration. *Animal Genetics*, 50(2), 182–186. Available from: https://doi.org/10.1111/age.12765

Yudianto, A., Sosiawan, A., Sulistyorini, N., Furqoni, A.H., Masjkur, I.N. & Setiawan, F. (2022) Relationship analysis of sibling pairs on Madurese ethnicity in Surabaya, using 12 STR loci for the paternity test process. *Journal of International Dental and Medical Research*, 15(4), 1608–1613.

SUPPORTING INFORMATION

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