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Variants in the Tyrosinase (*TYR*) Gene are Associated with Coat Color in the Dromedary (*Camelus Dromedarius*)

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ABSTRACT

Coat color genetics has been studied in many mammalian species. However, in the dromedary camel, there are only few efforts reported three genes that associated with coat color (*MC1R*, *ASIP* and *KIT*). Saudi dromedaries vary in color from white, light brown, brown, dark brown and black. Tyrosinase (encoded by *TYR* gene) is a key enzyme responsible for converting tyrosine to melanin in the melanin pathway. *TYR* is known as the *albino* locus as it causes albinism in several mammalian species. *TYR* variants are also associated with diluted coat color phenotypes in rabbits and mice. Here, we investigated the possibility of *TYR* contribution in the dromedary coat color variations. Dromedary *TYR* exon 1 gene was studies in the dromedary and two SNPs were detected at position c.200 C>T associated with shoulder height in one study and suggested to be associated with coat color and c.523 T>C associated with black dromedaries. Here, we sequenced *TYR* all coding regions and identified 3 single nucleotide polymorphisms (SNPs) in exon 1, 2 and 3 respectively. Our finding shows that *TYR* c.200 C>T is significantly associated with light brown coat color phenotype in the dromedary ($P<0.05$) suggesting codominant inheritance. This variant substitutes a proline with leucine at position 67 (p.P67L). Two synonymous SNPs variants were discovered in exon 2 c.861 G>A and exon3 c.950 C>T. The finding will contribute to the generation of coat color genetic test in the species.

Key words: Dromedary, Coat color, Genetics, TYR, Camelids.

INTRODUCTION

Coat color is one of the most important characteristics in domestic animals due to commercial, production and aesthetic purposes. It shows historical and geographical differences between breeds. Furthermore, coat color differs between population and subpopulations which has led to increase genetic diversity between domestic species (Andersson 2001).

Mammalian coat color is also a genetic trait governed by a few major pigmentation genes, and further modified by a larger number (over 350) of dilution and spotting genes (Cieslak et al. 2011; Ortolani et al. 1996). While mammalian color phenotypes are influenced by many genes, the type, amount, and distribution of the main pigments are regulated by just a few, specific genes. Among these, the two key genes are *melanocortin 1 receptor* (*MC1R*) and *agouti signaling protein* (*ASIP*) (Suzuki 2013). These two genes play the major role in regulating the production of black/brown pigment (eumelanin) and red/yellow pigment (pheomelanin) (Suzuki 2013). These pigments, eumelanin and pheomelanin, are produced by melanocytes which are the pigment cells.

Importantly, since the pigment cells are derived from the embryonic neural crest, mutations in pigmentation genes frequently cause pleiotropic effects involving sight, hearing and neurologic functioning (Bellone 2010). For example, certain hypopigmentation phenotypes in dromedary camel, alpacas, cats and dogs are associated with congenital deafness (Strain 1996; Kaas 2005; Jackling et al. 2014; Holl et al. 2017), while certain spotting patterns in horses (appaloosa) are associated with congenital night blindness (Fritz et al. 2014).

Variants of the *tyrosinase* gene (*TYR*) have been reported to affect coat color phenotypes in many mammalian species (Seruggia et al. 2021). Disfunction of TYR leads to albinism due to its enrollment in converting tyrosine to L-dihydroxy-phenylalanine (DOPA) and DOPA to DOPA quinone in melanin pathway production (Lai et al. 2018; Jia et al. 2021; Seruggia et al. 2021). Furthermore, *TYR* variations are associated with diluted

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coat color phenotypes in cattle, dog, and mice (Guibert et al. 2004; Saif, Iftekhar et al. 2020; Seruggia et al. 2021).

Saudi Arabia has twelve dromedary breeds that vary in color and distributed over the country (Abdallah and Faye 2012; Almathen et al. 2022). Dromedary camel coat color varies from white/cream, light brown, brown, dark brown and black coat color (Almathen et al. 2018; Alshanbari et al. 2019). Several coat color genetics reported *MC1R*, *ASIP*, and *KIT proto-oncogene, receptor tyrosine kinase* (*KIT*) are associated with different coat color phenotypes in the dromedary (Holl et al. 2017; Almathen et al. 2018; Alshanbari et al. 2019). Moreover, *TYR* gene exon 1 was studied two variations were reported in exon 1 at position c.200 C>T and c.523 T>C (Ishag et al. 2013; Alam et al. 2015; Mahmoud et al. 2020). Ishag et al. (2013) reported that c.200 C>T is associate with shoulder height. The other two reports suggested the C allele is associated with dark coat color in the dromedary (Mahmoud et al. 2020). Recent study shows TYR expression in white dromedary is significantly lower than other color phenotypes (Sheikh et al. 2021).

Dromedary camel coat color competitions provide significant awards to winners who have the most pure and best morphological characteristics camels. These awards are sponsored by the Saudi Arabian government (King Abdullaziz award, yearly) and others such as companies that interested in dromedary camel breeding systems. With little knowledge about dromedary coat color genetics, it is essential to understand coat color genetics in the species and provide coat color genetic test for the species. Here, we investigate the possible contribution of *TYR* gene and its involvement with coat color phenotypes in the dromedary.

MATERIALS AND METHODS

Ethical Approval

Samples were collected from Qassim University Veterinary animal hospital during veterinarian physical visit. Sample collection did not cause suffering to animals. Therefore, there is no need to Institutional Animal Ethics approval.

Animals and Phenotypes

We sampled 123 dromedaries originating from 7 different Saudi Arabian breeds. Coat color phenotypes were determined by visual inspection, recorded in written notes and/or photos, and were as follows: white/cream/ (n=32), light brown (n=22), brown (n=28), dark brown (n=21), black/dark brown (n=20) (Fig. 1). Even though these colors are from different breeds, we classify their color phenotypes under these five color groups. Table S1 presents summary information for all animals, breeds, phenotype, and genotype.

Samples

Blood was collected by jugular venipuncture into EDTA-containing Vacutainers (Becton Dickinson).

DNA Isolation

Genomic DNA was isolated from peripheral blood lymphocytes using Gentra Puregene Blood Kit (Qiagen) following the manufacturer's protocol. We evaluated DNA quality and quantity by NanoDrop 2000 spectrophotometer (Thermo Scientific) and by 1% agarose gel electrophoresis.

Primers, PCR and Sequencing

We used the available sequence information for the dromedary *TYR* in NCBI[1], UCSC[2], and Ensembl[3] genome browsers, and Primer3 software (Untergasser et al. 2012) to design primers as shown in Table 1. The sequence regions include all *TYR* 5 exons including the entire open reading frame (ORF) part of 3' untranslated region (UTR) and exon-intron punditries (Table 1). One primer set was used from Anello et al. (2019) study (Anello et al. 2019). PCR was conducted in 25µL reactions containing 50 ng dromedary genomic DNA and 1 unit of JumpStart Taq ReadyMix (Sigma Aldrich). PCR products were checked on a 1% agarose gel stained with ethidium bromide, purified by PEG precipitation, and sequenced by Macrogen Inc., Korea.

Sequence Analysis and Mutation Discovery

For initial mutation discovery, we sequenced PCR products of *TYR* in 6 white, 4 light brown, 8 brown, 2 dark brown and 4 black dromedaries. Sequences were analyzed for mutations using Sequencher v 5.4.6 software (Gene Codes Corp.). Effects of single nucleotide changes and indels on protein structure and function were evaluated with PolyPhen-2 toolkit (Adzhubei et al. 2013). Amino acid sequences of different species were retrieved from NCBI[5] and Ensembl[6]. We used ExPasy webtools (Gasteiger et al. 2003) to translate genomic sequence into protein and Transmembrane Protein Topology with a Hidden Markov Model (TMHMM) (Moller et al. 2001) to determine *TYR* transmembrane domains. Comparative analysis of the *TYR* protein across species was performed by aligning amino acid sequences in ClustalW (Thompson et al. 1994).

Large Cohort Genotyping and Association Analysis Putative causative mutation in *TYR* was further analyzed for genotype-phenotype association by Sanger sequencing that included 123 dromedaries for exon 1 and 70 dromedaries for exon 2.

Statistical Analysis

We conducted contingency analysis with JMP Program v12 (JMP®, Version 17. SAS Institute Inc., Cary, NC, 1989-2007) to examine the relationship between color phenotypes and genotypes at each variable site. Map manager was used to analyze the association of TYR gene he standard Chi-square test and R square (Nikulin 1973; Meer et al. 2002).

RESULTS

Phenotype Characterization

Coat color of Saudi dromedary camels is uniformed and varies from white to black. Darker coat color breeds show darker to black wool and hair on the hump, back of the neck and on the tail (Fig. 1). Due to different breed names, we classify coat color phenotypes based on the

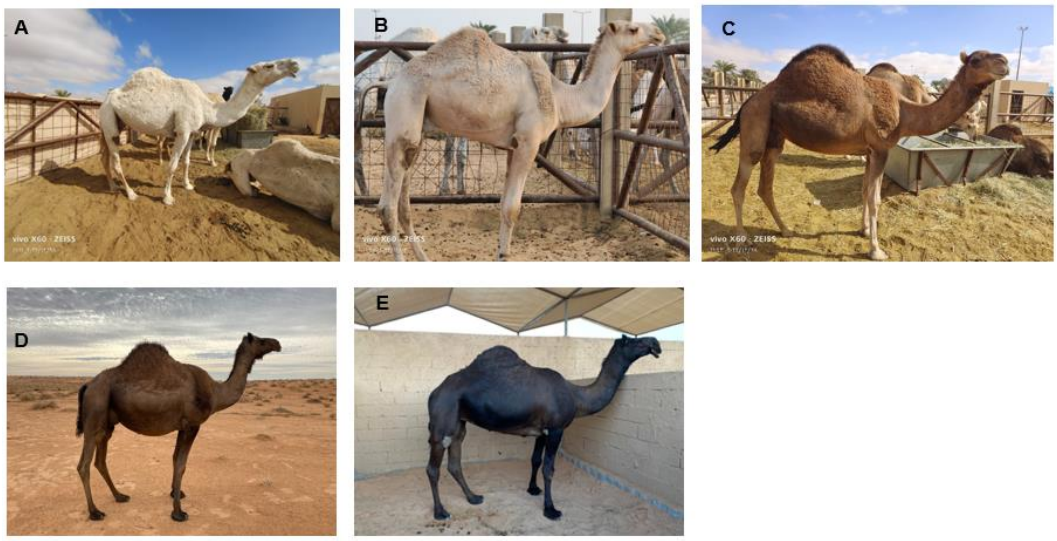

Fig. 1: Dromedary camel coat color phenotypes: A: White, B: Light brown, C: Brown, D: Dark brown, and E: Black.

Table 1: Primer design for amplifying dromedary TYR exons:

Primer name	Primer sequence (5'-3')	Target	Amplicon length (bp)	Target Region
TYREX1-F	CTCCTGGCTGCTTTGTACTG	Exon 1	954	819 bp exon 1 ORF* and 120 of intron 1
TYREX1-R	GAGCTCTTGACAGGGGACAT			
TYREX2-F*	ACCTGGAGGAGGAGACAGCA	Exon 2	402	50 bp intron 1, 218 exon 2 ORF* and 185 intron 2
TYREX2-R*	ACCCCGCTAGGGTTATTGGC			
TYREX3-F	GTCAGGCTTTCAATTGTAGTCG	Exon 3	315	104 bp intron 2, 147 bp exon 3 ORF* and 57 bp intron 3
TYREX3-R	TGAAGAAGTGCCAACCAACC			
TYREX4-F	AGTGAGCTTCATCAAGGCCT	Exon 4	599	189 bp intron 3, 182 bp exon 4 ORF and 223 bp intron 4
TYREX4-R	CACGGTTGCCATACACGAAA			
TYREX5-F	AGTGACAATAGTAGGAACACTGAGA	Exon 5	704	41 bp of intron 4, 227 bp exon5, 432 bp 3' UTR*
TYREX5-R	AGGATTATTATCGCCACCGTCA			

*ORF indicates open reading frame or coding sequence, these primers are used from Anello et al. (2019) and UTR: untranslated region.

color. Fig. 1 shows differences between dromedary camel phenotypes.

TYR Sequencing and SNPs Discover

TYR gene consists of 5 exons and 4 introns similar to other mammalian orthologs. We sequenced the five exons and exon-intron boundaries for initial SNPs discovery on 6 white, 4 light brown, 8 brown, 2 dark brown and 4 black. We identified a missense SNP (c.200 C>T) in exon 1, synonymous SNPs in exon 2 (c.861 G>A) and exon 3 (c.950 C>T) respectively (Table 2).

Structural Analysis

Due to the low quality of dromedary TYR protein sequences, we translated dromedary genomic *TYR* reference sequences and obtained 531 amino acid sequences using ExPasy tools. Exon 1 variant c.200 C>T replaces proline with leucine at position 67 (p.P67L). PolyPhen-2 shows that exon 1 missense variant (c.200 C>T) damages the protein with score of 0.98 where 1 is the worse score possible. Position 67 is located in the outside of TYR domain (Fig. 2). Fig. 2 also shows that TYR transmembrane domain is located in the end of the protein and the corresponding coding sequences are located in exon 5. Dromedary TYR protein sequences are highly conserved across mammalian species including Bactrian camel, llama, cattle, horse, and human. Multiple alignment sequences analysis shows that proline at position 67 is highly conserved across species suggesting it is important position for the protein function (Fig. 3).

We constructed a phylogenetic tree of TYR domain of dromedary TYR p.P67L and dromedary reference sequence and other mammalian TYR proteins. The tree shows that dromedary TYR protein is almost identical to dromedary reference and other camelids species, whereas chicken is the most different (Fig. 4). The tree also shows that ruminants are closer to camelids than horses and other mammalian species (Fig. 4). The tree suggests that our statistical analysis is robust.

Association Analysis

Association analysis shows significant association between exon 1 c.201 C>T with 24 dromedary camel coat color ($P< 0.05$) (Table 2). We further sequenced a total of 123 dromedary camels for exon 1 validate the association (Table 3). Significant association was observed between exon 1 c.200 C>T and light brown coat color ($P< 0.03$) suggesting codominant inheritance. Genotype frequency of CC is greater than 0.58 in white, brown and dark brown, whereas TT genotype is greater in light brown (Table 3). Black dromedaries on the other hand, have the greatest observed heterozygosity among other dromedary color groups (Table 3). Allele frequency of the C allele is higher in white, brown, dark brown, and black dromedaries, whereas the T allele is higher in light brown dromedaries (Table 3).

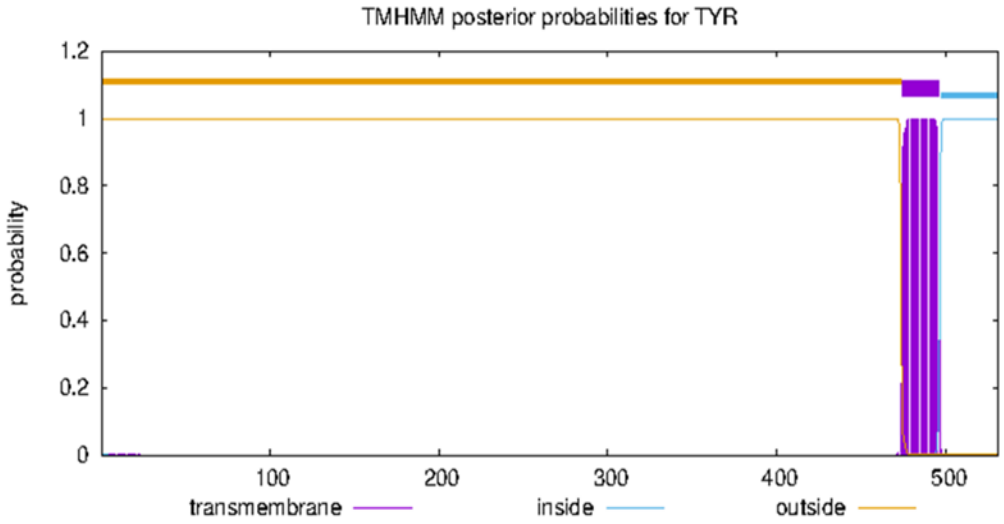

Fig. 2: TYR protein functional domains. TYR has only one transmembrane domain; y-axis: the probability of the amino acid sequences to be cytoplasmic (Gamboge), extracel-lular (blue), or part of the transmembrane helix (purple); x-axis: amino acid sequence. We used Transmembrane Protein Topology with a Hidden Markov Model (Moller et al. 2001; https://services.healthtech.dtu.dk/service.php?TMHMM-2.0).

Fig. 3: Comparative alignment of TYR amino acid sequences in diverse mammalian. The p.67 position is indicated by a yellow box; horizontal arrow shows the p.67 P > L mu-tation in the dromedary. Note that Proline is highly conserved across species.

Table 2: Sequence polymorphisms in TYR gene

Variant	*TYR* Location	Effect on protein	White	Light brown	Brown	Dark brown	Black	P-value
c.201 C>T	Exon 1	Missense	5CC, 1CT	3CT, 1TT	7CC, 1CT	1CC, 1CT	1CC, 3CT	<0.05
c.861 G>A	Exon 2	Synonymous	5GG, 1GA	3GG, 1GA	7GG, 1GA	1GG, 1GA	1GG, 3GA	<0.05
c.950 C>T	Exon 3	Synonymous	1CC, 4CT, 1TT	1CT, 3TT	3CC, 1CT, 4TT	1CC, 1TT	1CC, 2CT, 1TT	>0.05

Table 3: Genotype and allele frequencies of TYR exon 1 c.200 C>T missense mutation in large cohort association (n=123)

Coat Color	Genotype Frequency			Allele Frequency	
	CC	CT	TT	C	T
White (n=32)	0.56 (18)	0.38 (12)	0.06 (2)	0.75	0.25
Light brown (n=22)	0.32 (7)	0.5 (11)	0.18 (4)	0.57	0.43
Brown (n=28)	0.61 (17)	0.36 (10)	0.03 (1)	0.79	0.21
Dark brown (n=21)	0.62 (13)	0.29 (6)	0.09 (2)	0.76	0.24
Black (n=20)	0.3 (6)	0.6 (12)	0.1 (2)	0.8	0.2

Another significant association is observed in exon 2 at position c.861 G>A with 24 dromedary camel coat color (P< 0.05) that is synonymous (Table 2). To validate this association, we sequenced a total of 70 dromedary camels to validate the association. However, there was no significant association between exon c.861 G>A and dromedary coat color phenotypes (P>0.05). Our data shows that exon 1 and exon 2 variants are in perfect linkage disequilibrium (in the exception of 2 individuals) whereas exon 3 is further.

Poly T repeat was found in intron 2 that all of our sequences show a heterozygous deletion within the repeat.

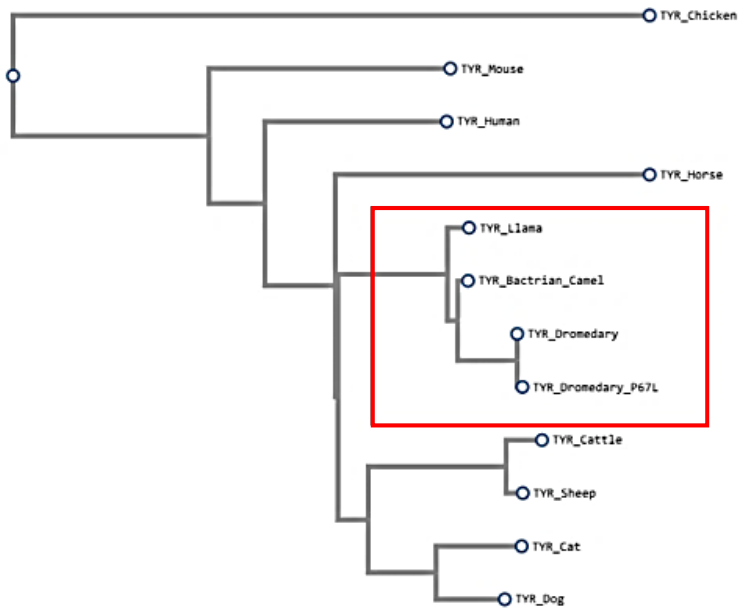

Fig. 4: A phylogenetic tree of dromedary TYR p.P67L and other 10 mammalian species and a chicken. The tree is constructed using ClustalW web tools. Camelid species are highlighted by a red box.

Another repetitive sequence was found in intron 3. These two repeats made it difficult to sequence exon 3. There was no correlation between the c.950 C>T in exon 3 and dromedary coat color phenotypes (P>0.05, Table 2). This variant did not change the amino acid sequence (synonymous). Furthermore, we did not observe genomic variants in exon 4 nor exon 5.

DISCUSSION

Saudi dromedary camels are classified into 12 different breeds many of these breeds share similar coat color patterns (Abdallah and Faye 2012; Almathen et al. 2022). Earlier studies suggested dromedary of Saudi Arbia should be classifies into 3 coat color groups where one of these studies combined dark brown and black to be one group and the other combined dark brown with brown (Almathen et al. 2018; Alshanbari et al. 2019). Other studies classified dromedaries based on the breeds where these breeds are known for certain coat color (Mahmoud et al. 2020). However, coat color phenotypes should be classified to the visual appearance of coat color. Therefore, we categorize the color phenotypes into five groups based on the amount of pigment in the skin. This also will increase the accuracy of our statistical analysis.

Our primary purpose of this study is to investigate *TYR* gene contribution in dromedary coat color. Dromedary *TYR* genomic structure is similar to other species orthologs, and the protein sequences are highly conserved across many species. We have identified only three variants in the coding region, where no variant discovery was observed in exon 4, 5, nor intron/exon boundaries (Table 2). Exon 1 c.200 C>T was discovered before, but investigators focused on population differences between dromedary breeds (Alam et al. 2015; Ishag et al. 2013; Mahmoud et al. 2020; Nowier et al. 2020). Moreover, these reports studied only exon 1 of *TYR* gene. It was reported that exon 1 has an extra variant at position c.523 C>T (Mahmoud et al. 2020); however, this variant was not detected in our analysis.

Our analysis showed that exon 1 c.200 C>T is significantly associated with diluted coat color in the dromedary (P<0.03). We showed that T allele frequency is higher in the light brown coat color than other dromedary coat color groups. This SNP leads to the substitution of proline to leucin at position 67 (Pro67Lue). This position is highly conserved across many mammalian species (Fig. 3). A SNP is detected in dog *TYR* gene at position c.230 G>A leads to an amino acid substitution of arginine to glutamine at position 77 (p.R77Q) that is associated with Hemalaiin coat color in dogs (light brown phenotype) (Bychkova et al. 2021). Another report shows that a missense mutation at position c.235 T>C of the *TYR* gene substituted a serin by proline at position 79 (p.S79P) leads to diluted coat color in rats (Kuramoto et al. 2010). Another report shows that several alleles of *TYR* are associated with lighter phenotype in mice (Challa et al. 2016). Moreover, mink *TYR* has a missense mutation at position c.1835 C>G (p.H420Q) results a diluted coat color (Benkel et al. 2009). Cat TYR also have a missense variant in exon 1 that leads to change glycine to tryptophan (p.G227W) that is associated with Himalayan coat color phenotype (Lyons et al. 2005).

Loss of TYR function caused by missense, nonsense, or frameshift mutations leads to albinism in different species (Oetting 2000; Schmutz et al. 2004; Blaszczyk et al. 2005; Imes et al. 2006; Anistoroaei et al. 2008). On the other hand, other *TYR* variants are associated with hypopigmentation in many mammalian species as described above. Therefore, we have very strong evidence that dromedary *TYR* c.200 C>T is associated with light brown coat color. Our data also suggests that light brown coat color in the dromedary shows a recessive mode of inheritance. Mammalian coat color genetics is a complicated trait due to many genes involved in regulating melanin synthesis and transportation.

We also found another two synonymous variation exon 2 and exon 3 respectively. However, there was no significant association between these variants and coat color phenotypes, nor these variants change amino acid

residues. It is worth mentioning exon 1 and 2 are in perfect linkage disequilibrium whereas exon 3 is further apart. Our results show that *TYR* genetic variation is lower comparing to other mammalian species. In contrast, 9 variants were identified in the *TYR* of Bactrian camel and 17 variants were found in the *TYR* of llama (Ming et al. 2016; Anello et al. 2019). It was reported that dromedary camel genetic variations are extremely low comparing to other mammalian species (Almathen et al. 2016).

Conclusion: We showed that *TYR* gene is associated with diluted coat color in the dromedary. We also showed that *TYR* exon 1 and exon 2 are linked. *TYR* exon c.200 C>T can be used as a genetic marker for testing for coat color in the dromedary.

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