

Tyrosinase (*Tyr*) Gene Mutation in Albino Mongolian Gerbil (*Meriones unguiculatus*)

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Abstract

Tyrosinase is encoded by the *Tyr* (*c* or *albino*) locus and is the key enzyme in pigment biosynthesis. Loss of function of this enzyme caused by gene mutation results in albinism. Most cases of albinism are caused by missense mutations of tyrosinase. Albino mutations in *Tyr* have been identified in various animals, including human, mouse, rat, rabbit, cattle, cat, and ferret, but not in gerbil. We created two new gerbil strains: MON/Num/a (inbred agouti phenotype) and MON/Num/c (albino phenotype). Here, we report that four nucleotide substitutions in the *Tyr* gene caused two missense mutations in amino acids in the albino gerbil: a G-to-A mutation at position 204 in exon 1 caused R77H, and A-to-G at position 1392 and G-to-T at position 1393 in exon 5 caused Q473R. The substitution at position 1408 in exon 5 was silent. These missense mutations are conserved in all albino phenotypes we tested. Therefore, we suggest that these mutations are responsible for albinism in gerbil.

Keywords

Tyrosinase (*Tyr*) Gene, Mongolian Gerbil (*Meriones unguiculatus*), Albino

1. Introduction

The Mongolian gerbil (*Meriones unguiculatus*) is extensively used as an animal model in studies of pharmacology [1], parasitology [2], aging [3], oncology [4], and reproduction [5] [6]. Gerbils used in scientific research originated from 20 pairs captured in the basin of the Amur River in eastern Mongolia and were imported into Japan in 1935. They were sent to the Kitasato Institute for rickettsial studies [7]. Agouti gerbils in our laboratory have been kept as a closed colony since 1983 from their origins at Tokyo Women's University and Tokyo University of Agriculture [6]. By repeated sub-mating of these gerbils, we have created the inbred agouti strain MON/Num/a (**Figure 1(A)**).

In addition, albino gerbils were introduced from Chiba City Zoo, and their phenotype has been maintained in the heterozygous state by sub-mating with MON/Num/a gerbils. After repeated sub-mating, we established a closed colony of MON/Num/c albino gerbils (**Figure 1(B)**).

In general, albinism is an autosomal recessive disorder, which occurs as a consequence of mutations in genes involved in regulating melanin biosynthesis [8] [9]. Many albino mouse strains (e.g., A, AKR, BALB/c, and ICR) lack pigmentation owing to mutations in the *Tyrosinase* (*Tyr*) gene [10]. Tyrosinase encoded by *Tyr* is well known as the key enzyme in pigment biosynthesis in mammals and is the first enzyme in the melanin synthesis pathway, converting tyrosine to dihydroxyphenylalanine (DOPA) and then to dopaquinone [11] [12]. Albinism caused by mutations in *Tyr* has been characterized in human [13], mouse [10] [14] [15], rat [16], rabbit [17], cat [18], ferret [19], and cattle [20]. The first report of complete albinism (*cc*) in gerbil was published by Matsuzaki *et al.* [21]. Additionally, some coat-color phenotypes (e.g., black chinchilla medium, *aac^{chm}c^{chm}*; siamese, *aac^{chm}c^h*; dark-tailed white, *aac^hc^h*; recessive yellow, *ee*; black recessive yellow, *aaee*; and fading recessive yellow, *e^fe^f*), considered to be related to *Tyr* mutations, have been reported [22] [23]. However, genetic evidence of albino mutation in gerbil has not been characterized yet.

Here, to identify the gene responsible for albinism in gerbil, we analyzed the cDNA sequence of the *Tyr* gene in albino phenotype gerbil (MON/Num/c) and compared it with that of wild-type gerbils (agouti, MON/Num/a; and MON/Jms/GbsSlc).

2. Materials and Methods

2.1. Animals

MON/Num/a (n = 5), MON/Num/c (n = 4), and MON/Jms/GbsSlc (n = 5) gerbils were used in this study. MON/Jms/GbsSlc gerbils were purchased from Japan SLC Inc. (Shizuoka, Japan). The gerbils were maintained at 22°C ± 3°C with lighting from 0700 to 1900 h (12 light:12 dark) and were given food pellets (Labo MR Stock, Nosan

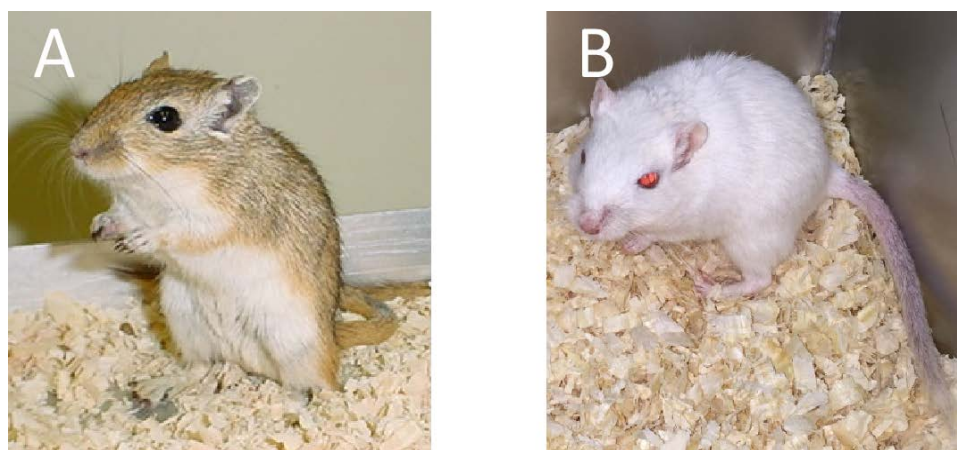


Figure 1. External characteristics of (A) MON/Num/a (agouti) and (B) MON/Num/c (albino) gerbils.

Corporation, Kanagawa, Japan) and water *ad libitum*. All of the procedures used here were reviewed and approved by Nihon University's Animal Care and Use Committee (AP14B078).

2.2. Determination of *Tyr* cDNA Sequence in Gerbil

Gerbils were euthanized with carbon dioxide. Total RNA was isolated from the eye with a Trizol reagent kit (Invitrogen Life Technologies, CA, USA) according to the manufacturer's protocol. RT-PCR was performed with an RNA PCR Kit (AMV) v. 2.1 (Takara, Shiga, Japan) according to the manufacturer's instructions. Three primer sets for sequencing gerbil *Tyr* cDNA were designed from highly conserved regions of mouse (BC079678), rat (NM001107535), and human (NM000372) *Tyr* cDNAs (Figure 2, Table 1). PCR consisted of an initial denaturation for 2 min at 94°C; 40 cycles of 30 s at 94°C, 1 min at 60°C, and 1 min at 72°C; and a final extension for 5 min at 72°C. The PCR products were electrophoresed in 1.5% agarose gels and stained with ethidium bromide. The fragments were purified and sequenced directly with a BigDye Terminator v. 3.1 Cycle Sequencing Kit (Applied Biosystems, CA, USA) in an ABI PRISM 310 genetic analyzer (Applied Biosystems).

2.3. Sequence Analysis

Each determined nucleotide and predicted amino acid sequence was aligned for comparison with mouse, rat, and human counterparts by ClustalW multiple alignment [24], and homology was calculated from the p-distance in MEGA 4 software [25].

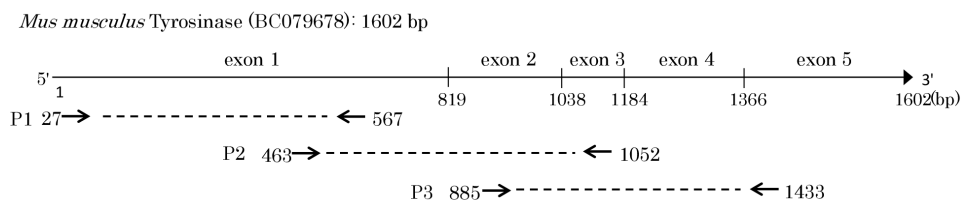


Figure 2. Nucleotide positions of primer sets.

Table 1. Primers used for the present sequencing gerbil *Tyr* gene.

Primer		Sequence	Product Size (bp)	Amplification region
		5' → 3'		
P1	F	TCTGTGGAGTTTCCAGATCT	541	Exon 1
	R	AAGCAGTGTGTCCCTTGACA		
P2	F	ACCTATGGCCAAATGAACAA	571	Exon 1-3
	R	AGTGGACTGGCAAATCCTTC		
P3	F	ACCACTATTACGTAATCCTG	549	Exon 2-5
	R	AGCCATGGCCAGATACGACT		

3. Results

3.1. Coat Color of Each Strain

MON/Num/a has the typical agouti (wild-type) phenotype characterized by dorsal hairs with a gray base, a yellow center band, and black tips. The belly and paws are creamy white. A demarcation line between dorsal and ventral side is present. The eyes, claws, and tip of the tail are black (**Figure 1(A)**). These characteristics are similar to MON/Jms/GbsSlc. MON/Num/c has a pure white coat and red eyes. Nose, ears, feet, and tail are covered with pure white hairs. A demarcation line between dorsal and ventral side is absent (**Figure 1(B)**).

3.2. Determination of *Tyr* cDNA Sequences

The cDNA sequences of *Tyr* in MON/Jms/GbsSlc (GenBank accession no. LC177618), MON/Num/a (LC177619), and MON/Num/c (LC177620) were determined (**Figure 3**). The 1408-bp sequences encoded 469 amino acids (**Figure 4**), and corresponded to part of the exon 1-to-5 regions of counterparts in other species, equivalent to 87.9% of the complete mouse (BC079678) *Tyr* cDNA and 88.4% of rat (NM001107535). *Tyr* cDNA and amino acid sequences of MON/Jms/GbsSlc and MON/Num/a matched completely in the region that we determined (**Figure 3**, **Figure 4**).

3.3. Comparison of *Tyr* Gene among Three Gerbil Strains and Other Species

Comparison of *Tyr* cDNA sequences between agouti (MON/Num/a and MON/Jms/GbsSlc) and albino gerbils (MON/Num/c) revealed four nucleotide substitutions: G-to-A at position 204 in exon 1, A-to-G at position 1392 in exon 5, G-to-T at position 1393 in exon 5, and C-to-A at position 1408 in exon 5 (**Figure 3**). The nucleotide substitution at position 204 caused an R77H alteration, and those at positions 1392-93 caused a Q473R alteration (**Figure 4**). That at position 1408 was silent. The *Tyr* cDNA sequence of agouti gerbil (MON/Num/a and MON/Jms/GbsSlc) showed >90% identity at the nucleotide and amino acid levels with those of mouse and rat, and >84% with those of human (**Table 2**).

4. Discussion

Albinism in gerbil was first reported by Matsuzaki *et al.* [21], but not since, and genetic evidence of albino mutations has not been characterized yet. Oculocutaneous albinism (OCA), which is a group of autosomal recessive diseases in humans and other animals, is characterized by reduced or absent melanin in skin, hair, and eyes. Type 1 OCA (OCA1) results from mutations in the *Tyr* gene, which codes for tyrosinase, a copper-containing enzyme that catalyzes the first two steps in the melanin biosynthesis pathway: the hydroxylation of tyrosine to DOPA and the subsequent oxidation of DOPA to dopaquinone [26]. It is well known that OCA1 is caused by nonsense, missense, frameshift, or splice-site alterations in *Tyr*. Various mutations causing OCA1 have been reported. In human, a single-base C-to-A substitution in exon 3, which causes a

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MON/Jms/GbsSlc, MON/Num 1 TCTGTGGAGTTTCCAGATCTCTGCTGGCCATTTTCTCGAGCCTGTGCTTCCTCTAAGAA
MON/Num/e 1 . . . . .

MON/Jms/GbsSlc, MON/Num 61 CCTGATGGCAAAGAATGCTGCCACCATGGATGGGTGATGGGAGTCCCTGCGGCCAGCT
MON/Num/e 61 . . . . .

MON/Jms/GbsSlc, MON/Num 121 TTCAGGCAGAGGTTCTGTTCAGGACATCCTTCTGTCCAACGCACCATCTGGACCTCAATT
MON/Num/e 121 . . . . .

MON/Jms/GbsSlc, MON/Num 181 CCCCTTCAAGGGGGTGGACGACCGTGAAGTTGTGGCCCTCTGTGTTTTATAATAGGACCTG
MON/Num/e 181 . . . . . A . . . . .

MON/Jms/GbsSlc, MON/Num 241 CCAGTGCTCTGGCAACTTCATGGGATTCAACTGCGGAAACTGTAAATTTGGATTTGGGGG
MON/Num/e 241 . . . . .

MON/Jms/GbsSlc, MON/Num 301 TCCAAACTGTACAGAGAAGCGACTCTCAATTAGAAGAAACATCTATGATTTGAGTGTCTC
MON/Num/e 301 . . . . .

MON/Jms/GbsSlc, MON/Num 361 GGAAAAGAATAGGTTTTTTTCTTACCTCACTTTATCAAAGCATACCATCAGCCCAGACTA
MON/Num/e 361 . . . . .

MON/Jms/GbsSlc, MON/Num 421 TGTCATCCCTACAGCCACCTACGGCCAAATGAACAATGGGTCAACACCCATGTTTAATGA
MON/Num/e 421 . . . . .

MON/Jms/GbsSlc, MON/Num 481 TATAAGCATCTATGATCTCTTGTATGGATGCATTACTATGTGTCAAGGGACACACTGCT
MON/Num/e 481 . . . . .

MON/Jms/GbsSlc, MON/Num 541 CGGAGGCTCCGAAATCTGGAGGGACATTGATTTTGCCACGAAGCCCAGGGTTTCTGCC
MON/Num/e 541 . . . . .

MON/Jms/GbsSlc, MON/Num 601 TTGGCACCGACTTTTCTTGCTACTGTGGGAACAAGAAATACAGGAACTAACTGGGGATGA
MON/Num/e 601 . . . . .

MON/Jms/GbsSlc, MON/Num 661 GAACTTCACCATTCCGTA CTGGGACTGGAGGGATGCAGAGAGCTGTGACATTTGTACAGA
MON/Num/e 661 . . . . .

MON/Jms/GbsSlc, MON/Num 721 CGATTACTTGGGCGCCATCACCTGAAAACCCTAACCTGCTCAGCCCAGCGTCTTTTT
MON/Num/e 721 . . . . .

MON/Jms/GbsSlc, MON/Num 781 CTCCTCCTGGCAGATCATTGTCAGCAGGTGAGAAGAGTACAATAGCCGTGAGGTTTTATG
MON/Num/e 781 . . . . .

MON/Jms/GbsSlc, MON/Num 841 CGATGGAACACCGGAAGGACCACCTGTTACGAAATCCTGGAAACCATGACAAAGCCAAAAC
MON/Num/e 841 . . . . .

MON/Jms/GbsSlc, MON/Num 901 CCCAGGCTCCCATCTTCAGCAGATGTGGAATTTTGTCTGAGTTTGACCCAGTATGAAAC
MON/Num/e 901 . . . . .

MON/Jms/GbsSlc, MON/Num 961 TGGATCAATGGATAGAAATTCCAATTTTCTGCTCAGAAACACGCTGGAAGGATTTGCCAG
MON/Num/e 961 . . . . .

MON/Jms/GbsSlc, MON/Num 1021 TCCACTCACAGGAATAGCAGATTTCTTCTCAGAGCAGCATGCACAATGCTTTGCATATCTA
MON/Num/e 1021 . . . . .

MON/Jms/GbsSlc, MON/Num 1081 TATGAATGGAACAATGTCTCAAGTCCAGGGATCAGCCAATGATCCCATTTTTCTTCTTCA
MON/Num/e 1081 . . . . .

MON/Jms/GbsSlc, MON/Num 1141 TCATGCTTTTGTGGACAGTATTTTTGAACAATGGCTCAGAAGACACCGCCCTCTCTAGA
MON/Num/e 1141 . . . . .

MON/Jms/GbsSlc, MON/Num 1201 AGCTTACCCAGAAGCCAATGCACCCATTGGCCATAACAGGGACTCCTACATGGTTCCTTT
MON/Num/e 1201 . . . . .

MON/Jms/GbsSlc, MON/Num 1261 TATACCGCTGTACAGAAATGGTGATTTCTTCATTTTCATCCAAGAATCTGGGATATGACTA
MON/Num/e 1261 . . . . .

MON/Jms/GbsSlc, MON/Num 1321 CAGCTACCTACAAGAATCAGATGCAGGCTTTTACAGAACTATATTGAGCCCTACTTGA
MON/Num/e 1321 . . . . .

MON/Jms/GbsSlc, MON/Num 1381 CCAAGCTAGTCAGATCTGGCCATGGCTC
MON/Num/e 1381 . . . . . GT . . . . . A
    
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Figure 3. Alignment of *Tyr* cDNA sequences in gerbils. Nucleotide substitutions between agouti and albino strains are highlighted. Gen-Bank accession numbers: MON/Jms/GbsSlc *Tyr*, LC177618; MON/Num/a *Tyr*, LC177619; MON/Num/c *Tyr*, LC177620.

MON/Jms/GbsSlc	1	-----LWSFQISAGHFPRACASSKNLMAKECCPPWMDGSPCGQLSGRGSCQDILL
MON/Num/a	1	-----.....
MON/Num/c	1	-----.....
Mouse	1	MFLAVLYCL.....D.....L.....
Rat	1	MFLAVLYYL.....T.....D.....H.....
Human	1	MLLAVLYCL.....T.....V.....E.....S.....R.....N.....
MON/Jms/GbsSlc	61	SNAPSGPQFPFKGVDDRELWPSVFYNRTCQCSGNFMGFNCGNCKFGFGGPNCTEKRLSIR
MON/Num/a	61
MON/Num/c	61H.....
Mouse	61	S.....S.....VL.....
Rat	61S.....L.....
Human	61L.....T.....S.....W.....R.....LV.....
MON/Jms/GbsSlc	121	RNIYDLSVSEKNRFFSYLTLSKHTISPDYVIPTATYGQMNGSTPMFNDISIYDLFVWMH
MON/Num/a	121
MON/Num/c	121
Mouse	121	F.....K.....A.....SV.....G.....N.....
Rat	121	F.....A.....K.....A.....SV.....G.....K.....N.....
Human	121	F.....AP.....DK.....A.....A.....S.....IG.....K.....N.....
MON/Jms/GbsSlc	181	YYVSRDTLGGSEIWRDIDFAHEAPGFLPWHRLFLLLWEQEIQELTGDENFTIPYWDWRD
MON/Num/a	181
MON/Num/c	181
Mouse	181R.....V.....
Rat	181M.....
Human	181M.....A.....A.....A.....R.....K.....
MON/Jms/GbsSlc	241	AESC DICTDDYLGGHHPENPNLLSPASFFSSWQIICSRSEEYNSRQVLC DGTPEG PLLRN
MON/Num/a	241
MON/Num/c	241
Mouse	241	N.....E.....R.....H.....
Rat	241	N.....E.....R.....E.....H.....
Human	241	K.....E.....M.....Q.....T.....V.....L.....H.....S.....N.....R.....
MON/Jms/GbsSlc	301	PGNHDKAKTPRLPSSADVEFCLSLTQYETGSM DRNSNFSFRNTLEGFASPLTGIADSSQS
MON/Num/a	301
MON/Num/c	301
Mouse	301S.....TA.....P.....
Rat	301S.....TA.....
Human	301SR.....S.....KAA.....A.....
MON/Jms/GbsSlc	361	SMHNALHIYMNGTMSQVQGSANDPIFL LHAFVDSIFEQWLR RHRPLLEAYPEANAPIGH
MON/Num/a	361
MON/Num/c	361
Mouse	361F.....V.....
Rat	361V.....
Human	361Q.....V.....
MON/Jms/GbsSlc	421	NRDSYMPVFPFIPLYRNGDFFISSKNLGYDYSYLQESDAGFYRNYIEPYLDQASQIWPWL
MON/Num/a	421
MON/Num/c	421R.....
Mouse	421T.....D.....P.....E.....R.....
Rat	421E.....D.....P.....E.....R.....
Human	421E.....D.....D.....PDSFQD.....KS.....E.....R.....S.....

Figure 4. Missense nucleotide mutations in the *Tyr* gene in albino gerbil cause R77H and Q473R alterations. GenBank accession numbers for encoding genes: MON/Jms/GbsSlc *Tyr*, LC177618; MON/Num/a *Tyr*, LC177619; MON/Num/c *Tyr*, LC177620; mouse *Tyr*, BC079678; rat *Tyr*, NM001107535; human *Tyr*, NM000372.

Table 2. Homologies between the gerbil and other mammals in the *Tyr* gene and its amino acids. Nucleotide and amino acid sequences were compared with mouse *Tyr* (BC079678), rat *Tyr* (NM001107535), and human *Tyr* (NM000372).

	Gerbil (MON/Num/a and MON/Jms/GbsSlc)	
	Nucleotide homology (%)	Amino acid homology (%)
Mouse	91.5	93.6
Rat	91.5	93.8
Human	81.1	86.4

T373K alteration, is frequently found [27]. In BALB/c mouse, a G-to-C mutation at position 387, which causes a C85S alteration, is common [14] [15]. In albino rat, a single G-to-A mutation at position 896 in exon 2 causes an R299H alteration [16]. In the cattle, a frame-shift mutation caused by an insertion in codon 316 is associated with complete albinism [20]. The absence of codon 325 in the domestic albino cat causes a premature stop codon [18]. In the white New Zealand rabbit, complete albinism is due to a missense alteration at residue 373 [17]. As these reports show, most albino mutations in mammals result from a missense or frameshift mutation in *Tyr*. In albino gerbil, on the other hand, we find two missense mutations (R77H encoded in exon 1 and Q473R encoded in exon 5) in tyrosinase (Figure 4), which are conserved all albino gerbils we tested. Therefore, we suggest that both missense mutations of *Tyr* are conserved in the albino phenotype and are responsible for albinism in gerbil. The gerbil is commonly used as a model animal in studies of a wide range of infectious diseases by reason of its high sensitivity to various parasite [2] and pathogens [1]. However, the mechanism of these sensitivities remains to be identified. So far, we have reported molecular information on immunoglobulin [28] [29] and variation in the IgG subclass [30] in the agouti (MON/Num/a) strain to investigate acquired immunity in gerbil, and have established methods for producing gerbil mAb [31] and cytokines [32] with heterohybridoma techniques. Although immune systems have not been compared in detail between albino (MON/Num/c) and agouti strains yet, use of the albino strain for immunological research may further contribute to the establishment of new strains as models of infectious disease.

In this study, we identified two missense mutations in exons 1 and 5 of the *Tyr* gene in albino gerbil. These mutations support the functional significance of tyrosinase in albinism in gerbil. However, we did not determine the full *Tyr* cDNA sequence in gerbil. As a next step, phenotypic characterization of albino-by-agouti crosses is needed to clarify how these missense mutations result in albinism. Our results will provide valuable information on albinism in gerbil and will contribute to the establishment of albino strains.

Conflict of Interest

The authors declare that there is no conflict of interest that could be perceived as preju-

dicing the impartiality of the research reported.

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