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Sequence Diversity of *MAOA* Gene within Wild and Docile Animal Species

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Abstract

Background: Molecular characterization of *MAOA* gene was performed to investigate aggressive behaviour within wild (lion, leopard, and wolf) as opposed to docile animal (sheep, goat) species living in different habitats, by undertaking sequence diversity analysis of this gene.

Methods: The *MAOA* gene was partially amplified by PCR for wild and docile animal species. Amplified DNA was sequenced and then analyzed using BioEdit and Sequencher softwares, while multiple sequence alignment and phylogenetics analysis were conducted through MEGA software. Bioinformatics tool like Prosite scan, Motif Scan and Prot Param were used to study properties of mutant proteins of *MAOA* gene.

Results: Different polymorphic sites were observed which included c.956, c.1063 in docile animals and c.2530 in wild animals. Phylogenetic analysis based on this candidate gene endorsed the existing taxonomy of subject animals, while bioinformatics tools explored the altered characteristics of mutant *MAOA* protein.

Conclusion: The newly found polymorphic loci in wild and docile animals in this study could have a role in behavioral response and acclimatization within their peculiar habitats. This study also highlights the genetic diversity of *MAOA* gene, which will add knowledge to the existing animal genetic resource of Pakistan.

Introduction

MAOA enzyme involved in oxidative deamination reactions, which is responsible for controlling behavioral attributes of the animals by degrading the neurotransmitters [1]. This gene is located on X chromosome with total of fifteen exons in *Capra hircus* (goat) as well as in *Ovis aries* (sheep). Its product is also found in liver, placenta and gastrointestinal tract. Serotonin, a hormone controlled by this gene is a neuromodulator that is linked with wide range of physiological functions in the central nervous system such as mood swings (mostly good moods) [2]. Absence of this gene has a negative impact leading to depressive behavioral patterns.

This gene has been selected as it greatly influences the behavior of living being. Presence of this protein regulates serotonin while its absence, down regulation or loss of functioning of this gene through manipulation or mutational event may lead to aggression, anxiety, fear, substance abuse and irregular sexual maturation [3]. Mostly, wild animals have much aggression as compared to domestic animals. This is because of their nature to acclimatize themselves according to their environment but genetic factor also plays role in controlling behavioral moods of subject species. Purpose of current study is to characterize and find out the *MAOA* gene variants contribution with the aggressive and docile behavior of the animals [4].

We obtained blood and skin samples for DNA extraction through proper channel from wild animals like leopard, markhor, wolf and tiger from the zoo veterinarians during treatment procedure and markhor samples from license holder safari agents. Similarly, docile animals of goat and sheep blood were collected from the local farmers and government livestock farms to search out whether the aggressive behavior of these animals has any relationship with the variants of this gene. We follow this approach by comparing functional domain encoding exons of this gene in various species to identify changes that would help them to adapt to their natural habitat. In-silico characterization was also performed on *MAOA* protein considering these genetic variants [5].

Methods

Sample Collection

Samples of wild animals (Rawal Tiger, Sam Tiger, Mohini Tigress, Wild Leopard and Markhor) were collected from Lahore zoo and license holder agents respectively, while samples of docile animals (Mungli sheep, Lehri, Angora, Kamori and Teddy goat breeds) were collected from local farmers and breeder. 5-10 mL of blood was obtained from jugular vein of each selected animal in EDTA containing Falcon tube [6].

DNA Extraction

DNA was extracted using standard inorganic method [7]. Later on, DNA concentration was also estimated through agarose gel electrophoresis at 80 volts for 40 minutes and standard concentration of 50ng/uL of DNA was used for downstream process.

Primer Designing

Gene ID 101106401 of *MAOA* has 15 exons having its major domain on exon 8 and 15. While, ENSOART00000003319 identifier from ensemble depicts that flavin amine oxidase domain is also very important in docile animals. Primer3 tool was used to design the primers sets for the partial amplification of aforementioned docile animal accession and XM_007084354.1 for wild animals.

PCR optimization, DNA amplification and sequencing

PCR was run on wild and docile animal extracted DNA by using standard protocol for 35 cycles. Primer made for docile species was optimized at 61C^{o} whereas primer made for wild species was optimized at 59C^{o}. After it, PCR products were precipitated using EXOSAP (Exonuclease shrimp alkaline phosphatase) and sequenced using Genetic analyzer 3130xL [8].

Bioinformatics tools

All the sequences were aligned using online tools Blast2Sequence (www.ncbi.nlm.nih.gov), and for studying the mutational events from aligned sequences, Bioedit was used [9,10]. Phylogenetic analysis was performed using MEGA (Molecular Evolutionary Genetics Analysis) software. For studying characteristics of mutated protein in the respective species such as post translational modifications, Prosite scan tool was used which generated consensus pattern of that post translated site. To study physio-chemical properties

Prot Param tool was applied whereas conserved domains were observed by using Motif Scan [9,11].

Results

Mutational Analysis

After aligning the sequences from Sequencher software and NCBI Blast2Sequence tool, the resulting trimmed cleaned DNA bases were compared to that of reference genes of domestic animals *Ovis aries* and *capra hircus* genomes. The Coding DNA sequence was compared with the exon 8 in reference sample. Mutational analysis identified 6 haplotypes in domestic species. Mutant-1 of *MAOA* comprises of a deletion at position c.956 and polymorphism at position c.1017. This variant was only present in Mungli sheep sample-01. Mutant-2 of *MAOA* gene comprises of a deletion at position c.956. It is present in Mungli sheep sample-2 alone. Mutant-3 comprises of polymorphic loci at three different positions i.e. c.956, c.1012 and c.1063. It is only present in Lehri goat. Mutant-4 of *MAOA* gene comprises of a polymorphism at c.956 positions. It is present in two goat breeds only i.e. Kamori and Angora goat. Mutant-5 composed of polymorphisms at c.956 and c.1013 positions. It is present in 2 goat breeds i.e. Kamori-2 and Teddy-2. Mutant-6 of this gene comprises of polymorphisms at several positions including c.992, c.996, c.1002, c.1004, c.1005, c.1007, c.1011, c.1012 and c.1099. It is present only in Teddy goat-1.

For sequence comparison in wild species, the chosen reference sample was *Panthera tigris*. Upon aligning sequences from wild species exon 15 of *Panthera tigris*. Five different haplotypes were found**.** Mutant-1 of *MAOA* gene in wild species comprises a polymorphism at c.956 positions. It is present only in wild wolf. Mutant-2 with a polymorphism at position c.1063. It is present only in Markhor. Mutant-3 comprises of a mutation at c.2530 position in two species i.e. Tiger Rawal and Leopard. While mutant-4 comprises a mutation at position c.2528 in tiger Sam only. Mutant-5 appeared with a mutation at position c.2528 and c.2543 in Mohini Tigress.

Species	Breed name	DNA sequence Change	Amino acid change	Remarks
Ovis aries	Mungli 1	c.1017T>A	Same as reference	Synonymous
	Mungli 2	c.956A>Del	Same as reference	Synonymous
Capra hircus	Lehri Goat	c.956A>G	p.Gl> Arg	Non-Synonymous
		c.1012G>T	p.Glu>Arg	
		c.1063A>G	p.Iso>Val	
	Angora Goat	c.956A>G	p.Glu>Arg	Non-Synonymous
	Kamori Goat	c.956A>G	p.Glu>Arg	Non-Synonymous
	Kamori goat 2	c.956A>G	p.Glu>Arg	Non-Synonymous
		c.1063 A>G	p.Iso>Val	
	Teddy Goat	c.996G>A	--	--
		c.1002C>G		
		c.1004T>C		
	Teddy Goat 2	c.956A>G	p.Glu>Glu	Synonymous
		c.1063A>G	p.Iso>Iso	
Panthera tigris	Wild wolf	c.956A>G	Same as Reference	Synonymous
	Tiger Rawal	c.2530InsT	p.try> Gly	Frame shift
			p.Glu>Arg	
	Tiger Sam	c.2528 Ins T	p.Glu>Ser	Frame shift
	Mohini Tigress	c.2528 Ins T	p.Glu> Ser	Frame shift
		c.2543 C>Del	p.Cys> Val	
Panthera tigris	Wild Leopard	c.2530InsT	p.try> Gly	Frame shift
			p.Glu>Arg	

Table 1: Standard Nomenclature of *MAOA* variants in domestic and wild species illustrating the DNA sequence changes and amino acids variants.

Phylogenetic Analysis

Phylogenetic tree was constructed using Molecular Evolutionary and Genetic Analysis Software (MEGA). This helped in determining the taxonomical order and relation of one species with the other on the basis of partial *MAOA* gene sequencing by considering main functional domain of this protein. Constructed cladogram gives the insight about mutational events and closely related species on the basis of these polymorphisms. This phylogenetic analysis involved 13 nucleotide sequences among 11 species (tiger, wolf, leopard, markhor, wild camel, olive baboon, gorilla, fox, yak, cheetah and human) with 13 samples of wild species while remaining were obtained from databases. Evolutionary analyses were conducted by using MEGA7. Figure 1 shows the relationship among all species of wild, domestic and other species taken from databases. This cladogram represents that each of the breed of goat is arising from the common node bears negligible mutation in the study and thus is placed in the same clade. All the sheep species showed more mutational events than goat. The minimum value for

Physiochemical properties	Wild type	Mutant 1 (c.1017)	Mutant 2 (c.956)	Mutant 3 (c.956,c.1012, c.1063)	Mutant 4 (c.956)	Mutant 5 (c.956, c.1013)	Mutant 6 (c.956, c.1063)
No. of amino acids	53	125	126	76	130	130	127
Molecular weight	6298.6	14313.8	14370.9	9011.8	15096.8	15112.9	
Positive charged residues(Asp+Glu)	9	17	17	12	19	19	10
Negative charged residues(Arg+Lys)	3	9	9	5	11	11	15
Theoretical PI	9.76	9.54	9.54	9.55	9.34	9.34	9.62
Formula	$C_{289}H_{461}N_{75}O_{72}S_5$	$C_{649}H_{1027}N_{171}O_{175}S_9$	$C_{651}H_{1030}N_{172}O_{176}S_9$	$C_{412}H_{655}N_{107}O_{103}S_8$	$C_{677}H_{1085}N_{185}O_{182}S_{12}$	$C_{677}H_{1085}N_{185}O_{182}S_{12}$	$C_{624}H_{996}N_{188}O_{182}S_2$
No. of atoms	902	2013	2038	1285	2136	2141	1992
Extinction coefficient	10095 9970	18700 18450	18700 18450	11710 11460	13325 12950	13325 12950	10095 9970
Half life	1.2 hrs	100 hrs	100 hrs	1.2 hrs	1.2 hrs	1. hrs	30 hrs
Instability index	38.96	50.45	50.13	41.24	74.28	70.90	51.41
Aliphatic index	84.72	82.72	82.06	92.37	83.23	86.23	91.34
GRAVY	-0.255	-0.188	-0.190	-0.009	-0.288	-0.247	-0.263

Table 2: Physio-chemical properties of wild and mutant type of MAOA protein in domestic species through Prot Param tool

Physiochemical properties	Wild type protein	Mutant 1 (c.956)	Mutant 2 (c.1063)	Mutant 3 (c.2530)	Mutant 4 (c.2528)	Mutant 5 (c.2528,c.2543)
No. of amino acids	52	125	123	118	121	123
Molecular weight	2800.5	14313.8	4223.4	12969.9	13353.6	13306
Positive charged residues(Asp+Glu)	3	17	21	8	16	10
Negative charged residues(Arg+Lys)	6	9	6	7	7	9
Theoretical PI	4.92	9.54	10.15	7.84	9.89	7.71
Formula	$C_{253}H_{390}N_{72}O_{77}S_4$	$C_{649}H_{1027}N_{171}O_{175}S_9$	$C_{637}H_{997}N_{185}O_{174}S_6$	$C_{572}H_{885}N_{165}O_{161}S_{10}$	$C_{596}H_{966}N_{166}O_{169}S_6$	$C_{578}H_{901}N_{169}O_{175}S_9$
No. of atoms	796	2031	1999	1793	1903	1832
Extinction coefficient	11250	18700	25815	12990	12740	22500
Half life	1.1 hrs	100 hrs	30 hrs	1 hr	1 hr	1.1 hr
Instability index	84.17	50.45	67.97	83.87	47.22	59.47
Aliphatic index	76.73	82.72	71.22	76.78	95.87	72.20
GRAVY	-0.369	-0.188	-0.398	-0.103	0.199	-0.190

Table 3: Physio-chemical properties of wild and mutant type of MAOA protein in wild species through Prot Param tool

Motif Information of wild and mutant types		Position	Raw Score	N-Score	E-Value
Wild type of domestic species	Wild Type: LDL Receptor Class B	46-53	116	4.471	7.2e+02
	Nebulin repeat profile	45-53	105	4.079	1.8e+03
Mutants of Domestic species	M1 and M2: Bacterial Ig like domain 1	1-4	39	4.251	1.2e+03
	Nebulin repeat profile	45-54	112	4.262	1.2e+03
	M3, M4 and M5: Nebulin repeat profile	45-54	112	4.262	1.2e+03
	M6: *PFTA* Protein prenyltransferases alpha subunit repeat profile	120-127	220	4.28	1.1e+03
Mutant of Wild species	M1: Bacterial Ig like domain 1	1-4	39	4.25	1.2e+03
	Nebulin repeat profile	45-54	112	4.26	1.2e+03

*'?' in the status indicates that the questionable or the weak match is present. Further biological evidences are required to determine true or false negative status of the respective match. (M1: Mutant 1, M2: Mutant 2, M3: Mutant 3, M4: Mutant 4, M5: Mutant 5, M6: Mutant 6)

Table 4: The motif information of wild and mutant types MAOA protein in domestic and wild species showing the configuration and match scoring of the relevant sequences.

Sr. No.	Wild type and Mutants of *MAOA*	Post translational modification site	Position of amino acid modification site	Consensus Sequence
1	Wild type	Protein Kinase C phosphorylation site	13-15	[ST]-X-[RK]
2	M 1, M2,M4, and M5	Protein Kinase C Phosphorylation site	13-15	[ST]-X-[RK]
		Casein Kinase II phosphorylation site	81-84	[ST]-x(2)[DE] [SorTisthephosphorylationsite]
		N myristoylation site	97-102	G-{EDRKHPFYW}-x(2)-[STAGCN]-{P}[GistheN-myristoylationsite]
3.	M3	Protein Kinase C phosphorylation site	13-15	[ST]-X-[RK]
		Casein Kinase II phosphorylation site	67-70	[ST]-x(2)[DE] [SorTisthephosphorylationsite]
4.	M6	Protein Kinase C phosphorylation site	21-23	[ST]-X-[RK]
		Casein Kinase II Phosphorylation site	83-86	[ST]-x(2)[DE] [SorTisthephosphorylationsite]
		N-Glycosylation site	97-100	N-{P}-[ST]-{P}

Table 5: The post translational modifications of MAOA protein in wild and mutants of domestic species along with its consensus pattern that ordinarily showing the amino acids position.

Sr. No.	Reference and Mutants of MAOA gene	Post translational modification site	Position of amino acid modification site	Consensus Sequence
1	Wild type	Casein Kinase II phosphorylation site	10-13	[ST]-x(2)[DE] [SorTisthephosphorylationsite]
		N myristoylation site	34-39	G-{EDRKHPFYW}-x(2)-[STAGCN]-{P}[GistheN-myristoylationsite]
2	M 1 , M4 and M5	Protein Kinase C phosphorylation site	13-15	[ST]-X-[RK]
		Casein Kinase II phosphorylation site	81-84	[ST]-x(2)[DE] [SorTisthephosphorylationsite]
		N myristoylation site	97-102	G-{EDRKHPFYW}-x(2)-[STAGCN]-{P}[GistheN-myristoylationsite]
2.	M2	Protein Kinase C phosphorylation site	38-40	[ST]-X-[RK]
		N myristoylation site	30-35	G-{EDRKHPFYW}-x(2)-[STAGCN]- {P}[GistheN-myristoylationsite]
		N-Glycosylation site	65-68	N-{P}-[ST]-{P}
		Amidation site	42-45	x-G-[RK]-[RK]
3.	**M3**	Protein Kinase C phosphorylation site	49-51	[ST]-X-[RK]
		N myristoylation site	84-89	G-{EDRKHPFYW}-x(2)-[STAGCN]-{P}[GistheN-myristoylationsite]

Table 6: The post translational modifications of MAOA protein in wild and mutants of wild species along with its consensus pattern

percentage mutational event in this study was found to be of Kamori goat breed with teddy that is 0% whereas the maximum value was found to be of camel 12.96 with horse.

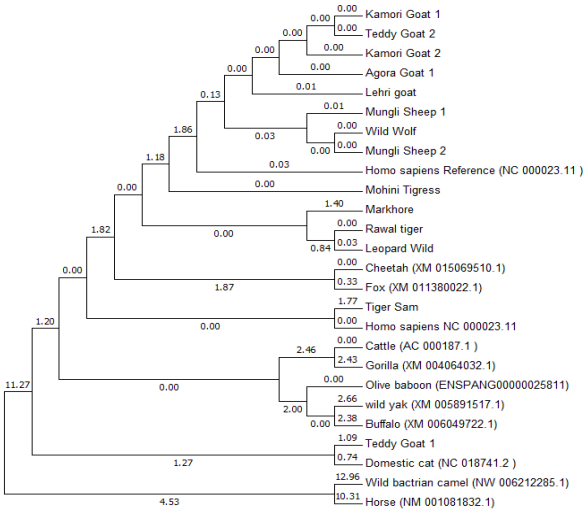

Figure 1: Molecular Phylogenetic analysis of wild and docile species by Maximum Likelihood method based on Tamura-Nei method (http://lifesciences.asu.edu/mep/)

Application of Bioinformatics Tools

Prot Param tool

Prot Param is an online bioinformatics tool which is used for observing the physiological features of protein. These properties help in better understanding the role of proteomics due to which species could have altered pathways hindering the metabolic activities.

Wild type of The "Extinction Coefficient" explains the amount of light that is absorbed by the protein. The half-life of a protein specifies the time when the protein is degraded into half after its synthesis. The "Aliphatic Index" indicates the volume occupied by the aliphatic side chains. Instability index describes stability of proteins in test tube, if value is above 40 than protein is unstable and results indicated that wild type is highly stable whereas mutant protein is unstable in our study. This stability of proteins might have an effect on behavioral characteristics of wild type as compared to docile animals. "GRAVY" indicates the hydrophobicity of the protein; high positive score indicates high hydrophobicity, while our results showed negative values.

Motif Scan tool

It (http://myhits.isb-sib.ch/cgi-bin/motif_scan) is another bioinformatics tool of great importance that gives information about different motifs present in the particular sequence of the protein. It allows the alignment and match scoring of the sequence with its database thus providing interpretation of the matched scores. Results in domestic species showed that LDL receptor class B is present in wild type of domestic species whereas mutants have Nebulin repeat profile in common. Results in wild species showed that wild type, Mutant 2,3,4 and 5 has no domain in it whereas one of the mutants i.e. M-1 has bacterial domain.

Prosite scan tool

It scans proteins for matches against the Prosite database of motifs as well as consensus patterns**.** Nascent protein undergoes post-translational modifications and becomes functional. Thus, it is necessary to study those modifications, this tool also provides the information about the post translational modifications.

Post translational modifications of the wild and mutant protein are shown in Table 5 and 6. Any one of the amino acids mentioned in this bracket "[ ]" may be present at this position, while an amino acid within"{}"shows that there can be any amino acid at that site except for the one indicated within the braces. Similarly, parenthesis "( )" shows the number of amino acids that should be present at a particular site and "x" shows any of the amino acids [12,13].

Discussion

Mutations were read after aligning the sequences from NCBI Blast2Sequece. Coding DNA sequence file of wild and docile species was made which helped in counting the base pairs at the position where polymorphisms were present [12]. Polymorphisms in two samples of Mungli breed were observed and it was found that both of them had deletion at 956 of coding position but this polymorphism had no effect on amino acid change. Glutamine protein was being converted into glutamine even after this polymorphism. Thus, it was regarded as synonymous mutation. Lehri goat had polymorphism at the same position. At c.956 position and 1063, Adenine was being converted into guanine (in both the cases), due to which glutamine changed into arginine (in the first polymorphism) and isoleucine changed into valine (in the second polymorphism). Angora goat, Kamori goat 1, Kamori goat 2, Teddy goat 1 and Teddy goat 2 had polymorphism at c.956 where 'A' was being changed into 'G' which affected the protein product due to

change in amino acid sequence. Glutamine was changed into arginine. These polymorphisms can be regarded as non-synonymous ones in coding region of exon no. 8 [14]. Similar mutations were found in a study of a point mutation within a codon in exon 8 of the human MAOA leading to a premature termination of protein which is associated with uncertain mental retardation as well as impulsive aggression, arson, attempted rape and exhibitionism in male members of a Dutch family [9].

Phylogenetic tree shows that Rawal tiger and wild leopard are closely related to one another on the basis of *MAOA* gene sequence. 0.03% mutational events are present in wild leopard. Markhore is the next related species present nearer to them with 2.7% (1.39+1.31) mutational events in it. Wild wolf and Mohini tigress have been originated from the same node and thus are sister groups with 2.09% mutational events. Wild Bactrian camel and Olive baboon has 2.80% mutation. This tree has been constructed based on the sequence of one gene rather than the whole genome. Still, these results could help guide phylogenetic analysis on the basis of whole genome given that MAOA the candidate gene in this study plays an important role in influencing behavior [11].

Prot Param tool was applied for analyzing the physio-chemical properties in domestic mutants. Wild type of MAOA Protein has least number of amino acids and Mutant 5 has the maximum molecular weight. Physio-chemical properties in this variant have been greatly affected. The "Extinction Coefficient" value for wild type and M6 was found to be same. The half-life for wild type, M3, M4 and M5 was same i.e. 1.2 hrs. Instability index indicated that wild type is highly stable whereas mutant protein is unstable [15]. The "Aliphatic Index" value for wild type, M1, M2 and M4 is same. "GRAVY", results showed negative values. Motif scan tool was used [16]. Nebulin repeat profile was found in wild type, M1, M2, M3, M4 and M5 whereas M6 had protein prenyl transferase alpha subunit repeat profile.

Sequence diversity analysis was performed on wild species. Four species (Tiger, Leopard, Markhore and wild wolf) of different species (Tiger Rawal, Sam tiger, Mohini tigress, Wild leopard, wolf and Markhor) were analyzed among wild animals. Polymorphisms in three breeds (Rawal tiger, Sam tiger and Mohini tigress) of one species (Tiger) were observed. The results showed that Rawal tiger and wild leopard had a polymorphism at coding position of c. 2530 in exon no. 15 in which the base changed into Thymine. This one base change had an adverse effect on protein product of both (Rawal tiger and Leopard) the species as reading frame was shifted [15]. Tiger Sam and Mohini tigress had a polymorphism at c. 2528 position in which the base changed into thymine and Glutamine amino acid was converted into serine [12]. A study was conducted in which three polymorphisms (rs909525,rs6323 and rs2064070) of the *MAOA* gene were found to be highly associated with aggression related traits in suicidal males, while the single nucleotide polymorphism(SNP) rs6323 was also found associated with anger in females [6]. These variations lead to a clue that this single gene, though present in both wild and docile species, is present in diversified form. Sequence diversity can be clearly observed within each wild and docile species.

Phylogenetic tree shows that Rawal tiger and wild leopard are closely related to one another on the basis of *MAOA* gene sequence. 0.03% mutational events are present in wild leopard. Markhore is the next related species present nearer to them with 2.7% (1.39+1.31) mutational events in it. Wild wolf and Mohini tigress have been originated from the same node and thus are sister groups with 2.09% mutational events. Wild Bactrian camel and Olive baboon has 2.80% mutation. This tree has been constructed on the sequence of one gene only. Whole genome sequence approach has not been used. So, these results would help in performing the phylogenetic analysis on the basis of whole genome sequenced including this candidate gene study [11].

Prot Param tool was applied for analyzing the physio-chemical properties in wild species mutants as well. Wild type of MAOA Protein has least number of amino acids i.e. 52. Mutant 1 has the maximum weight. The "Extinction Coefficient had the least value in wild type whereas Mutant 2 had the highest value [15]. The half-life for wild type, M3, M4 and M5 was same i.e. 1 hr. Instability index indicates that wild type is highly stable whereas mutant protein is unstable [16]. The "Aliphatic Index" value for wild type, M3 is same. "GRAVY" results showed positive value in M4 only. Extra post translational modification amidation site was found in wild species and this was absent in domestic in species.

CDS position c.956 was observed as common variant in docile species, while none of the position were found common among wild animals. Phylogenetic tree was constructed on the basis of these observed variants to have an insight of existing taxonomy of these animals. Observed variants in *MAOA* gene might be responsible for behavioral differences between wild and docile species and may be helpful in designing new studies for confirmation and to ascertain the association of these altered loci in the larger purview of systems biology.

Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

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