Monoamine Oxidase Polymorphisms in Japanese and rhesus macaques (*Macaca fuscata* and *M. mulatta*)

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ABSTRACT

Monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B) are enzymes that degrade several monoamines of the central nervous system and have long been implicated in the modulation of social behavior. Macaque monkeys are a suitable model for investigating the role of functional monoamine oxidase polymorphisms in behavior modulation given the high amount of social diversity among the nearly two dozen species. The present study reports allele frequencies for two polymorphisms, *MAOA-LPR* and *MBin2*, in samples of rhesus (*Macaca mulatta*) and Japanese (*M. fuscata*) macaques. Our results suggest that the two species may differ in high- and low-activity *MAOA-LPR* allele frequencies. Specifically, 89% of the Japanese macaque alleles in our sample were the low-activity variant, whereas only 41% of the rhesus macaque alleles were of this sort. In our samples, the two species possessed similar allelic variation at the *MBin2* locus, with each possessing some species-specific alleles. We also tested for associations between *MAOA-LPR* genotype and plasma serotonin (5-HT) and dopamine (DA) concentrations in a subset of rhesus macaques, which revealed no association with genotype. Our findings point toward potential differences in the monoaminergic system of two closely related macaque species.

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INTRODUCTION

- Japanese and rhesus macaques are estimated to have diverged between 0.31-0.88 million years ago[1] and they display similar social styles, as both species are highly despotic and aggressive relative to many other macaque species[2].
- Among Japanese macaques, regional differences in social tolerance have been observed[3]. They also form what are referred to as "cluster formations". This behavior helps them conserve body heat in cold climates and has been associated with increased social tolerance[4].
- To investigate the genetic basis of social style in Japanese and rhesus macaques, we focused on two genetic polymorphisms, *MAOA-LPR* and *MBin2*.
- *MAOA-LPR* is a VNTR promoter polymorphism of the *MAOA* gene, which encode the enzyme MAO-A. This enzyme degrades various neurotransmitter, including serotonin (5-HT) and dopamine (DA). *MAOA-LPR* alleles interact with rearing environment to influence aggression in rhesus macaques[5].
- *MBin2* is an intronic dinucleotide repeat polymorphism of the *MAOB* gene, which encode the enzyme MAO-B. This enzyme degrades DA in addition to other neurochemicals. Little is known about *MBin2*'s role in mediating aspects of social behavior.

METHODS AND MATERIALS

- Whole blood was used for direct PCR to target *MAOA-LPR* and *MBin2* loci
- ABI 3130 Genetic Analyzer was used for genotyping

Species	N		$N_{MAOA\text{-}LPR}$	N_{MBin2}
	female	male		
Japanese	17	21	55	55
rhesus	25*	18	68	64

*The number (N) of monkeys included in analyses, categorized by sex; $N_{MAOA\text{-}LPR}$: number of MAOA-LPR alleles; N_{MBin2}: number of MBin2 alleles. *while 25 rhesus monkeys were used in our examination of MAOA-LPR, only 23 were included in our MBin2 analysis due to unsuccessful genotyping of two rhesus monkeys, both female.*

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Japanese macaques are native to Japan, where they are adapted to the country's climate extremes

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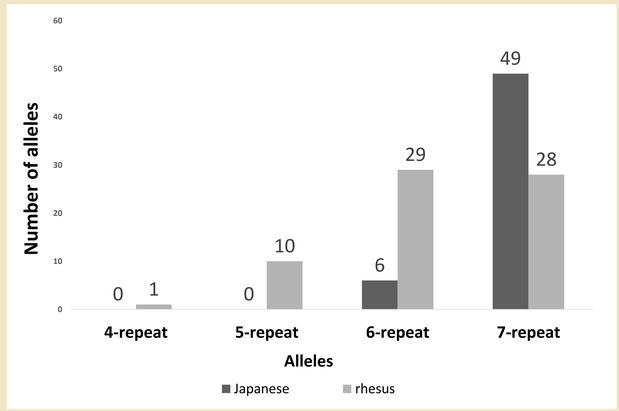
Rhesus macaques are widely distributed throughout south and southeast Asia, where they thrive in a variety of environments ranging from forested to urban

RESULTS

- Relative to rhesus macaques, Japanese macaques were less variable at the *MAOA-LPR* locus.
- While rhesus macaques possessed four alleles, with 41% being low-activity, Japanese macaques possessed two alleles, 89% of which were low-activity.
- The two species possessed similar allelic variation at the *MBin2* locus.
- In a small subset of rhesus macaques for which data were available, plasma 5-HT and DA concentrations were not associated with *MAOA-LPR* genotype.



Distribution of MAOA-LPR alleles: 4-, 5-, 6-, and 7-repeat alleles for MAOA-LPR correspond with 310, 328, 346, 364 bp fragment lengths obtained from genotyping. The activity of the 4-repeat allele is unknown, the 5- and 6- repeat alleles are high-activity, and the 7-repeat allele is low-activity.

DISCUSSION

- Japanese macaques are an island species, so the possibility that founders' effect has contributed to the observed allele frequencies must be considered. Even so, the high frequency of low-activity variants found in our Japanese macaque sample may partially underlie the recent observation of elevated plasma 5-HT in Japanese macaques relative to rhesus macaques[10].
- It has been suggested that the formation of large huddles likely requires increased social tolerance among group members. The role of 5-HT and genetic variants that impact the central serotonergic system, such as *MAOA-LPR*, have not be investigated in the context of cluster formations. Future studies on this topic may be insightful for elucidating environmental drivers of social and physiological plasticity in the Japanese macaque relative to other species.
- Future comparative neurobiological studies among macaque species, combined with the genetic data, will provide a more comprehensive view of the neurodiversity that may underlie the social complexity within the genus *Macaca*.

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- Image 6: National Geographic; Image 7: Getty Images; Image 8: National Geographic; Image 9: Encyclopedia Britannica
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