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Mitigating Chinese-Indian rhesus macaque (*Macaca mulatta*) hybridity at the California National Primate Research Center (CNPRC)

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Abstract

Background—The effectiveness of abating hybridity in a rhesus breeding colony was evaluated.

Methods—STR data from the 2006 to 2015 newborns were analyzed.

Results—Hybridity decreased over successive years. Birth cohorts retained high genetic variability without signs of inbreeding and differentiation.

Conclusions—Hybridity was minimized without compromising overall genetic variability.

Keywords

Genetic management; captive breeding; short tandem repeats; STRs; microsatellites

Introduction

Most domestic breeding facilities do not knowingly admix Chinese and Indian rhesus macaques; a notable exception is the California National Primate Research Center (CNPRC) [6, 9]. The CNPRC maximized genetic variation within its colony by introgressing Chinese alleles [6, 9, 11, 12] into its colony. However, Indian animals have remained in high demand from external investigators and requests for hybrids have declined. These factors and rising production costs compelled the CNPRC to ensure that only animals confirmed as pure Indian using molecular ancestry and pedigree analyses [5, 6] were used for derivation and colony expansion. Since 2006, Chinese and hybrid animals have been prioritized for sale or for terminal research in order to limit hybridity and to stabilize overall production and population growth. From 2010 onwards adult hybrid males were selectively vasectomized

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and since 2016 hybrid females were treated with Depo-Provera (contraceptive injections) for short term/temporary pregnancy prevention.

Halting hybridity from spreading by systematically eliminating Chinese and hybrid animals can potentially cause a loss of genetic variation. Maintaining variability is an important goal in genetic management as it ensures each animal's value in research. By increasing heterozygosity and minimizing homozygosity for deleterious alleles, genetic management ensures the entire colony's survivability and productivity.

In this study, genotypes from 14 short tandem repeat markers (STRs) were used to estimate the ancestry and genetic diversity of new birth cohorts starting in 2006. The study assessed whether mitigating hybridity has adversely affected colony genetic structure and composition by analyzing the genetic data of newborns during the 2006–2015 period.

Methods

The National Research Council Guidelines for Use and Care of Laboratory Animals were followed. Experimental protocols were approved by the UC Davis IACUC. STR genotypes for 6945 animals were generated using methods described in Kanthaswamy et al. [8]. Table 1 lists the number of newborns in each year that were analyzed. The identity of the birth cohort as well as the generation to which an animal belonged was used to investigate diachronic changes in genetic composition. Allele numbers (Na), observed heterozygosity (OH), expected heterozygosity (EH), inbreeding coefficient (FIS) and pairwise FST (to assess the degree of genetic differentiation among birth cohorts) estimates were computed using Arlequin v3.5.1.3 [1, 2, 19]. The significance of the pairwise FST estimates was determined with a probability distribution constructed from permutation tests (N = 1000) with Bonferroni corrections for multiple comparisons [16]. A Bayesian cluster approach to illustrate the genetic composition of the birth cohorts was applied using STRUCTURE v. 2.3.4 [3, 15]. Details on the analysis have been described elsewhere, Kanthaswamy et al. [8, 10] and Jiang et al. [4].

Results

Sample numbers, Na, OH, and EH values are presented in Table 1. It is known that increased inbreeding results in a deficit of heterozygotes. Although annual inbreeding (FIS, Table 1) measurements ranged from 0.03 in 2006 and 2007 to 0.01 in 2015, the different birth cohorts reflected comparable OH and EH. Na declined by two alleles on average; Na estimates show that 16.8 alleles were present in 2006 and then reduced to 14.3 alleles in the 2014 and 2015. In accordance with Wright [20], who suggested that values of FST within the range 0 to 0.05 indicate little differentiation, Table 1 reveals that FST among birth cohorts was negligible (range: 0 to 0.0023).

When ancestry estimates included all newborns within a birth cohort, the degree of Chinese ancestry (DCA) diminished five-fold from 0.148 in 2006 to 0.027 in 2015 (Table 1). When only the DCA of hybrids were considered, an Analysis of Variance (ANOVA) revealed a significant (p < 0.05) decline in DCA from 0.419 to 0.226 between 2006 and 2015 (Table 1 and Figure 1).

Discussion

This study shows that that serial attrition and replacement of Chinese and hybrid rhesus have been successful in reducing hybridity significantly during the 2006–15 period. The percentage of hybrids within field cages however have been shown to not have any apparent influence on FIS values [9]. As such, the three-fold decline in FIS across birth cohorts from 2006 (0.032) to 2015 (0.11) is probably caused by the removal of Chinese rhesus, many of whom are close relatives who descended from grandparents that were imported from China in the 1990s [13]. In cases where entire families of Chinese animals were housed (such as field cage NC17) [9], the disbanding of those animals would have had a greater impact on FIS values.

Intergenerational allelic and genetic diversity indices have remained largely stable with no genetic differentiation among birth cohorts. Pairwise FST estimates suggest that annual newborns have remained undifferentiated reflecting overlaps of common alleles among different birth cohorts. The birth cohorts retained mean Na, OH, and EH values that were approximately 60%, 8%, and 11%, respectively, more than the estimates generated from Indian origin animals at the Caribbean Primate Research Center (CPRC) [10]. These findings agree with colony-wide data from other breeding facilities that the CNPRC animals consistently displayed greater variation [14]. These observations suggest that serial attrition and replacement of these Chinese and hybrid rhesus have no adverse genetic impact on the colony.

Allele numbers have remained consistent for all but 2014 and 2015, suggesting that effects of genetic drift are probably taking hold by eliminating rare alleles. Closed breeding programs often experience drift and genetic loss [6, 7]. A solution to neutralize drift and replace lost alleles is to introduce animals of Indian descent from other facilities. The infant swap program pioneered by the CNPRC can further foster the distribution of variation throughout the breeding colony [17].

The genetic structure and composition of birth cohorts suggest that annual newborns have not genetically diverged. The genetic diversity of the birth cohorts is an important genetic resource for future breeding programs, which should be maintained in the CNPRC breeding stock. Molecular and pedigree analyses are important and useful in the genetic management of captive breeding colonies, and in the case of the CNPRC these approaches are critical for future breeding programs.

Acknowledgments

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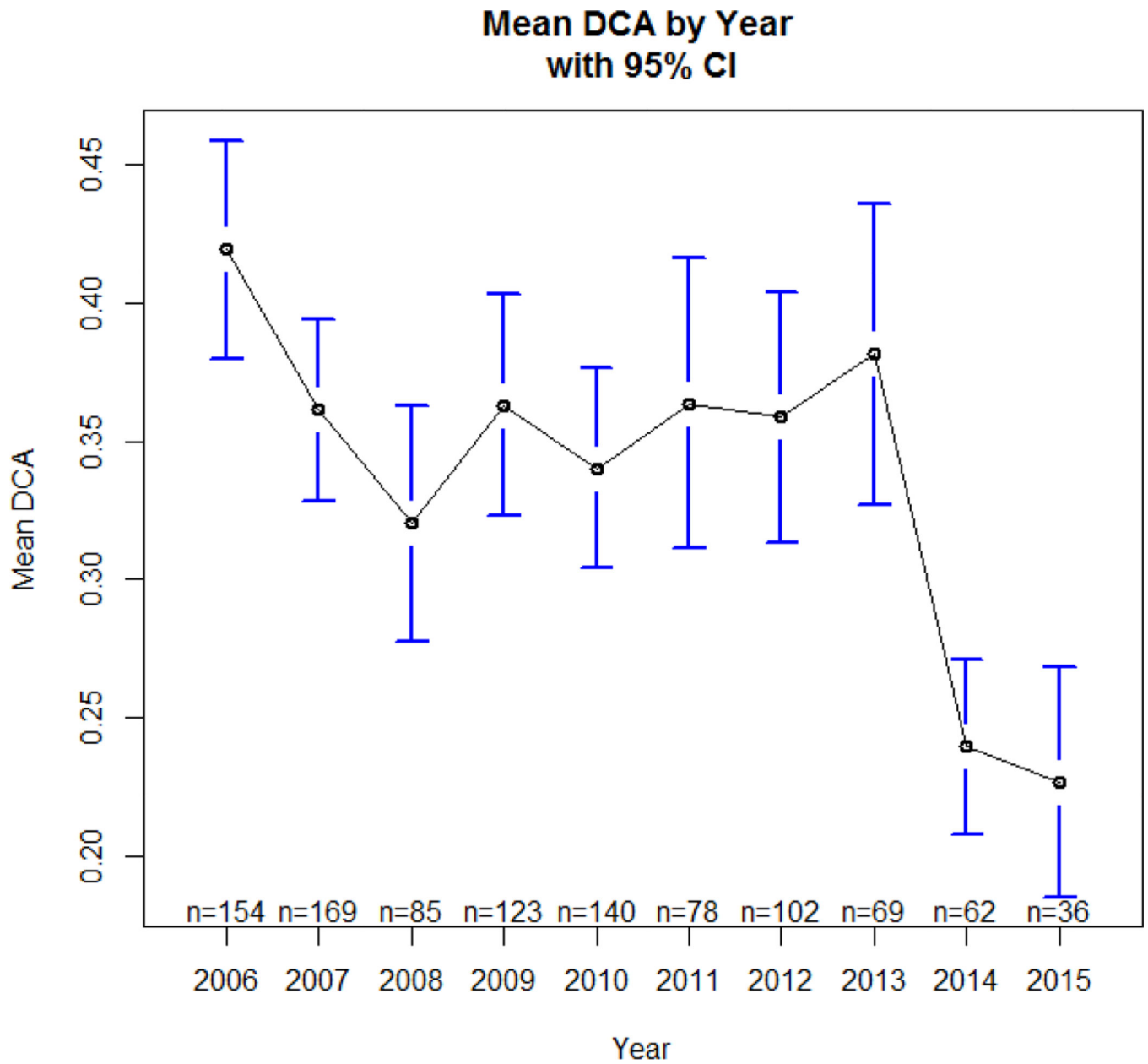
Figure 1.
ANOVA shows that annual DCA estimates among hybrids in 2014 and 2015 were significantly ($p < 0.05$) lower than 2006. n is hybrid sample number and CI is confidence interval. The graph was plotted using the gplots package in R [18].

Table 1

Sample numbers (N), allele numbers (Na), observed heterozygosity (OH), and expected heterozygosity (EH) estimates. Pairwise FST estimates are in *italics*. Degrees of Chinese ancestry (DCA) across birth cohorts are <u>underlined</u>; DCA estimates for hybrids only are in **bold** numbers.

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Mean estimates across birth cohorts
N	650	710	729	796	801	627	702	750	653	527	694.5
Na	16.8	17.4	16.9	17.1	16.6	16.5	16.4	16.6	14.5	14.3	16.31
OH	0.78	0.77	0.77	0.77	0.78	0.78	0.78	0.78	0.77	0.77	0.775
EH	0.80	0.80	0.79	0.79	0.80	0.79	0.80	0.79	0.79	0.78	0.793
FIS	0.032	0.032	0.026	0.025	0.023	0.017	0.027	0.016	0.024	0.011	0.0233
2006										**0.148**	<u>0.419</u>
2007	*0.0004*									**0.113**	<u>0.361</u>
2008	*0.0006*	*0.0002*								**0.073**	<u>0.320</u>
2009	*0.0010*	*0.0003*	*0.0001*							**0.085**	<u>0.363</u>
2010	*0.0008*	*0.0006*	*0.0002*	*0.0000*						**0.092**	<u>0.340</u>
2011	*0.0014*	*0.0007*	*0.0005*	*0.0007*	*0.0004*					**0.072**	<u>0.364</u>
2012	*0.0006*	*0.0005*	*0.0003*	*0.0008*	*0.0005*	*0.0003*				**0.080**	<u>0.359</u>
2013	*0.0010*	*0.0009*	*0.0006*	*0.0009*	*0.0008*	*0.0004*	*0.0004*			**0.068**	<u>0.382</u>
2014	*0.0019*	*0.0014*	*0.0011*	*0.0013*	*0.0013*	*0.0011*	*0.0009*	*0.0005*		**0.037**	<u>0.239</u>
2015	*0.0023*	*0.0017*	*0.0013*	*0.0011*	*0.0011*	*0.0010*	*0.0012*	*0.0011*	*0.0003*	**0.027**	<u>0.226</u>