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A Nonhuman Primate Model for the Out of Africa Theory Utilizing Chinese- and Indian-Derived Rhesus Macaques (*Macaca mulatta*)

Jacob N. Hunter

A thesis submitted to the faculty of
Brigham Young University
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Master of Science

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ABSTRACT

A Nonhuman Primate Model of the Out of Africa Theory Utilizing Chinese- and Indian-Derived Rhesus Macaques (*Macaca mulatta*)

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Master of Science

Evidence suggests that certain genotypic variants associated with novelty-seeking and aggressiveness, such as the 7-repeat dopamine D4 receptor variant (DRD4-7R), short (s) allele of the serotonin transporter (5-HTT), and the low-activity variant of the MAOa promoter (MAOa-L), are more prevalent in human groups that radiated out of Africa than human groups that remained in Africa. Rhesus macaques (*Macaca mulatta*), like humans, are a widespread species of primates that needed to adapt to different regional environments with one group, Indian- derived rhesus macaques, largely occupying predictable and resource-rich environments, while the other group, the Chinese-derived rhesus macaques, has come to occupy less predictable and resource-abundant environments. Rhesus macaques possess orthologues of these trait-related genes, making it possible to compare the frequency of genotypes associated with these traits between members of two strains. DNA was obtained from N=212 rhesus macaques (*n*=54 Chinese-derived, *n*=158 Indian-derived) and genotyped for DRD4 (*n*=98), 5-HTT (*n*=190), and MAOA (*n*=97). Analyses showed that Chinese-derived subjects exhibited higher frequencies of the DRD4-7R and 5-HTT-*s*-allele when compared to Indian-derived subjects. There were no strain differences in MAOA-L genotype groupings, but the Chinese-derived subjects exhibited a more frequent high-activity (MAOA-H-6R) allele when compared to the Indian-derived subjects. The results suggest that the Chinese-derived rhesus macaques possess a higher frequency of alleles associated with novelty-seeking, impulsivity, and aggressiveness compared to their Indian-derived peers and that those genotypically-mediated traits may have beneficial to both humans and rhesus macaques as they spread into novel and unfamiliar environments.

Keywords: 5-HTT, DRD4, novelty-seeking, aggressiveness, rhesus macaque

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The "Out of Africa" Theory

The genus *Homo* is unique among primates in its extensive migratory tendencies, with the paragon of this phenomenon exhibited by *Homo sapiens*. Yet the earliest *H. sapiens* discoveries have been unearthed in Ethiopia, and date from 195,000 years ago (McDougall et al., 2005), over 120,000 years before mankind began to spread throughout the world in the Out of Africa event. Moreover, an early wave of human emigration into the eastern Mediterranean met with failure, with those emigrants being replaced by Neanderthals (*Homo neanderthalensis*) once climate conditions worsened in the territories they had attempted to occupy (Garcea, 2012; Shea, 2003). Put simply, mankind, in a sense, was an endemic species in Africa, until between 50-70,000 years ago (Fernandes et al., 2012; Quintana-Murci et al., 1999; Tierney et al., 2017; Timmermann & Friedrich, 2016). Then, in a brief period of geological time, *H. sapiens* spread extensively within Africa (Rito et al., 2019) and beyond to occupy both the Old and New World (Cann et al., 1987; Stringer & Andrews, 1988).

The essential question emerges of which factors may have changed to allow our species to successfully expand throughout the world and outcompete other human species when the previous expansion of mankind that had failed. The expansion of humanity out of Africa was likely precipitated by number of factors, with possible contributing factors ranging from climate change (Carto et al., 2009; Derricourt, 2006; Finlayson, 2005) to advances in technology (Backwell et al., 2018; Brooks et al., 2006; Lombard, 2011; Wadley, 2010) to cultural shifts (d'Errico et al., 2017; d'Errico et al., 2005; Klein, 2008; Texier et al., 2010) and certainly any combination of these or other factors. While outside forces may have precipitated this radiation another important potential factor that has not received as extensive a focus in the Out of Africa framework is the role of behavioral differences, particularly stable responses to the outside world, otherwise referred to as traits. Expanding within, and eventually radiating out of Africa was a risky endeavor, and one in which traits such as novelty-seeking, impulsivity, and aggressiveness may have been beneficial in contributing to the initial exploration and later occupation of novel territories.

Temperament/Traits

A sizeable literature in animals makes a case for the role of boldness, novelty-seeking, and aggressiveness in the expansion of species. Studying crayfish, Pintor et al. (2008) found that invasive species that were introduced into novel streams engaged in a bold behavioral response, which while increasing the risk of predation, also provided more opportunities to feed, whereas other species would avoid such danger. Fraser et al. (2001) utilized a combined laboratory and field technique to determine that within a population of Trinidad killifish (*Rivulus hartii*), subjects that left the safety of cover sooner in a tank test were more likely to expand further in a river once they were released, and the difference between the low and high novelty-seeking subjects, was more pronounced when the authors selected rivers with a high degree of environmental risk. In laboratory experiments, common frog (*Rana temporaria*) tadpoles and froglets from the mainland scored lower on boldness tests than individuals whose ancestors colonized offshore islands (Brodin et al., 2012). Within nonendemic populations of house sparrows (*Passer domesticus*), researchers have identified that species that live further from the locus of introduction are more likely to explore unfamiliar stimuli (Liebl & Martin, 2012) and consume unfamiliar food sources (Liebl & Martin, 2014). Taken together, the studies suggest that traits of boldness and novelty-seeking may be beneficial in helping species modify their behavior to take risks and prosper in novel territories.

Aggressiveness is also an important component of successful dispersing species, enabling species scoring higher on this trait to outcompete other species for access to resources (Hudina et al., 2014). This association is rather robust, with evidence from crustaceans (Pintor et al., 2008; Weis, 2010) to reptiles (Polo-Cavia et al., 2010), birds (Dow, 2016; Duckworth, 2008; Duckworth & Badyaev, 2007), and mammals (Harris & Macdonald, 2007) confirming the role of aggression in species expansion. It appears that this combination of temperaments favoring high-risk, high-benefit behaviors may carry significant benefit to those possessing this repertoire as they come to occupy novel environments and it is reasonable to infer the same may have been valid for humanity as it radiated out of Africa.

Genetic Basis

Temperament, which is composed of traits, is considered to carry a significant genetic component, as evidenced by narrow sense heritability that falls between 0.2 and 0.6 (Fagnani et al., 2017; Planalp et al., 2017; Saudino, 2005; Shiner et al., 2012). Although it is impossible to directly assess the role of traits in the Out of Africa expansion, it stands to reason that genotypes associated with traits such as novelty-seeking, impulsivity, and aggressiveness may provide a window into the potential role of these traits in mankind's expansion into unfamiliar environments both within and outside Africa. Notable among these are variants at functionally-implicated genes such as the dopamine D4 receptor (*DRD4*), serotonin transporter (5-HTT, or *SLC6A4*), and monoamine oxidase A (*MAOA*).

Studies show that the low-functioning dopamine D4 receptor 7R variant (DRD4-7R) is associated with risk-taking (Carpenter et al., 2011; Dreber et al., 2009; Møller & Garamszegi, 2012), impulsivity (Congdon et al., 2008; Schilling et al., 2014) and impulsive aggression (Dmitrieva et al., 2011; Fresan et al., 2007; Schmidt et al., 2002) in humans. Its principal association, however, is with the trait of novelty-seeking (Ebstein et al., 1996; Fidler et al., 2007; Hejjas et al., 2007; Korsten et al., 2010; Momozawa et al., 2005). Several studies show a positive correlation between geographic distance from Africa and frequency of the DRD4-7R, suggesting that that the trait of novelty-seeking, with which this genotype is implicated, may have played a role in movements out of Africa (Chang et al., 1996; Chen et al., 1999; Matthews & Butler, 2011). Other studies show that within ethnic groups, the DRD4-7R is more common in those groups that travelled further from their locus of origin, when compared to groups that did not radiate as extensively (Chen et al., 1999). Furthermore, the DRD4-7R is less common in sedentary populations than it is in nomadic groups (Chen et al., 1999), where impulsivity and novelty-seeking may be adaptive in the challenging and resource-deficient environments that nomadic groups tend to occupy (Eisenberg et al., 2008; Jensen et al., 1997; Williams & Taylor, 2006). These studies suggest that DRD4-7R-mediated traits, such as novelty-seeking and of impulsivity, may have been adaptive in human groups that ventured nomadically out of Africa (Ding et al., 2002).

Polymorphisms in the upstream promoter regulatory region for the serotonin transporter (5-HTT) and monoamine oxidase A (MAOA) are frequently studied in relation to their purported contributions to aggressive and impulsive behavior. The promoter region for the 5-HTT is functionally biallelic, with an ancestral long (*l*) allele and a comparatively less functional short (*s*) allele (Bennett et al., 2002; Heils et al., 1996). Several studies suggest that the *s*-allele contributes to reactive and impulse aggression (Aluja et al., 2009; Beitchman et al., 2006; Retz et al., 2004) presumably via impairments in central serotonergic functioning (Bennett et al., 2002;

Reist et al., 2001), a well-known risk factor in impulsive behavior and aggression (Brown et al., 1979; Higley et al., 1996; Higley et al., 1992; Howell et al., 2007; Kruesi et al., 1990; Lidberg et al., 1985; Linnoila et al., 1983; Virkkunen et al., 1995; Virkkunen et al., 1987).

Monoamine oxidase-A (MAO) is an enzyme that is involved in the metabolism of serotonin, dopamine, and norepinephrine (Shih & Thompson, 1999). The promoter for its gene has several variants, grouped into two genotypes according to function: high functioning (MAOA-H) and low functioning (MAOA-L). Like the *s*-allele of the 5-HTT, the MAOA-L is frequently implicated in impulsive aggression (Beitchman et al., 2004; Gallardo-Pujol et al., 2013; McDermott et al., 2009).

Although both the 5-HTT and MAOA have received less attention in the Out of Africa framework than has the DRD4-7R, studies suggest the MAOA-L is common among groups that emigrated further from Africa, such as Asian populations, with a frequency approaching 0.70 among Chinese individuals (Way & Lieberman, 2010). The *s*-allele is also more frequent in groups that radiated out of Africa (Haberstick et al., 2015; Murdoch et al., 2013) and as with MAOA-L, is also particularly common in Asian populations (Chiao & Blizinsky, 2010; Gelernter et al., 1997; Mrazek et al., 2013). Although only correlational and unable to rule out effects of neutral selection on these allele distributions, these findings provide important evidence for studies investigating whether the phenotypic expression of 5-HTT and MAOA genotypes may have been of benefit to populations whose ancestors explored new environments out of Africa, as has been suggested for the DRD4-7R (Ding et al., 2002).

Rhesus Macaque Evolutionary History

The fragmentary nature of the archaeological record, as well as difficulties in determining to which human species fossils and archaeological remains belong, limits the ability to test associations between these trait-related genotypic variants and exploration and occupation of novel territories. Moreover, with the advent of air and other forms modern rapid travel, genetic isolation and slow predictable migratory patterns likely have been obscured. Orthologs of many of the human genetic variants, however, are present in species of our closest-living relatives, the non-human primates. One particular species, the rhesus macaque (*Macaca mulatta*) is particularly important in translational biomedical, genetic, and behavioral research because of its extensive shared ancestry and genetics with humans (Gibbs et al., 2007). Studies indicate that rhesus macaques possess orthologues for the DRD4 (Coyne et al., 2015), 5-HTT (Bennett et al., 2002; Wendland, Lesch, et al., 2006), and MAOA (Newman et al., 2005; Wendland, Hampe, et al., 2006), and the rhesus is frequently utilized to assess the relationship between these candidate genes and behavior (Barr & Driscoll, 2013; Coyne et al., 2015; Newman et al., 2005; Suomi, 2006). Studies suggest that the association between DRD4-7R and risk-taking is present in rhesus monkeys (Coyne et al., 2015). While the biallelic 5-HTT appears to have arisen independently in both human and rhesus macaque lineages (Lesch et al., 1997; Shattuck et al., 2014), studies suggest that it plays a role in behavioral adaptability (Shattuck et al., 2014), as well as aggression (Schwandt et al., 2010) in both species. The MAOA-L is likewise associated with aggressive behavior in rhesus monkeys, although this is often in the context of early parental neglect in both species (Karere et al., 2009; Newman et al., 2005).

Like humans, rhesus macaques are a geographically widespread primate species, occupying a vast swath of territory across much of continental Asia (Satkoski et al., 2008). The ancestral rhesus macaque likely emerged in the resource-abundant tropical jungles of Indochina, diverging from the closely-related long-tail macaque (*Macaca fascicularis*) and traveling north (Hasan et al., 2014; Hernandez et al., 2007;

Xue et al., 2016) where it split into two populations, one that occupied China, and another that traveled west into India and the Near East (Hasan et al., 2014; Kyes et al., 2006; Smith & McDonough, 2005; Wu et al., 2013; Xue et al., 2016). While the Indian-derived population occupied warmer areas with more predictable conditions (Koyama & PB, 1981; Kumar & Solanki, 2003; Kumar et al., 2011; Neville, 1968; Seth & Seth, 1985; Southwick et al., 1961; Southwick & Siddiqi, 1977; Wada, 2005), the ancestors of Chinese-derived rhesus macaques occupy a diversity of habitats, from tropical islands off the Chinese coast (Jiang et al., 1991) to resource-poor limestone cliffs (Tang et al., 2016) to frigid, dangerous, and resource-poor mountain ranges (Lu et al., 2007; Wenyuan et al., 1993; Xie et al., 2012). Prior work has demonstrated variability in genetics underlying morphological and physiological adaptations to both the cold and warm conditions Chinese-derived rhesus macaques occupy (Wu et al., 2013). Genetically-mediated behavioral traits that maximized behavioral flexibility, as well competitive ability over resources in agonistic encounters may have also been adaptive in the varied environments Chinese-derived rhesus macaques came to occupy, although this has not been previously assessed.

The Current Study

Given that rhesus macaques possess orthologues of human candidate genes associated with novelty-seeking, impulsivity, and aggressiveness, and given that the two strains of rhesus macaques exhibited differences in the habitats they came to occupy during their evolutionary history, rhesus macaques may provide a model for comparing the frequencies of these candidate genes between the two strains, to determine if parallels are present between groups of humans and rhesus macaques that colonized unfamiliar and potentially less-predictable territories. This is an important step in determining whether genetically-mediated traits such as novelty-seeking and aggressiveness may have been involved in the expansion of the two most-widely distributed species of primates on Earth. Shattuck et al. (2014) were the first to report a higher frequency of the *s*-allele in Chinese-derived rhesus macaque when compared to their Indian-derived counterparts, and other studies demonstrate both behavioral (Champoux et al., 1997) and temperament (Champoux et al., 1994) differences between the two strains. To the authors' knowledge, no studies have examined strain-mediated differences in DRD4 and MAOA genotypes. Thus, the present study assesses strain differences in the frequencies of DRD4-7R, 5-HTT *s*-allele, and MAOA-L in the Chinese- and Indian-derived rhesus macaques.

Hypotheses

It is hypothesized that, compared to Indian-derived monkeys, Chinese-derived rhesus macaques will exhibit a relatively higher frequency of the DRD4-7R, 5-HTT-*s*-allele, and MAOA-L.

Materials and Methods

Subjects

Subjects were 212 rhesus macaques (99 female, 113 male), genotyped for DRD4, 5-HTT, and MAOA. Subjects represented twelve birth cohorts from 1991-1992, and 1994-2003, and were housed at the National Institutes of Health Animal Center (NIHAC), located in Poolesville, Maryland, USA. In order to maintain genetic diversity within the colony, matings were planned and males were rotated between groups every three years. These measures resulted in an average identity-by-descent of 1.68%, approximately equivalent to the relatedness of third cousins, which others use as an acceptable criterion for outbred pedigree (Newman et al., 2005; Robin et al., 1997; Wood et al., 2020). Subjects were part of an established extended pedigree that ranges back to the 1950s, and the geographical origin was known for each of the founders. None of the founders came from the same region, indicating that the founders were unlikely to be related. Water was provided *ad libitum*, and monkeys were fed a diet of Purina® High Protein Monkey Chow (#5038), supplemented with fresh fruit three times a week and sunflower or other seeds, provided daily. All protocols were approved by the Institutional Animal Care and Use Committee of the National Institute on Alcohol Abuse and Alcoholism and the National Institute of Child Health and Human Development.

Genotyping

DNA was extracted from blood samples obtained during routine examinations when the subjects were infants, except for adults purchased as breeders, for which it was extracted in adulthood. While there was a total of 212 subjects, the sample size for each of the genotypes varied due to DNA availability at the time of sequencing: DRD4 (*n* = 98), 5-HTT (*n* = 190), and MAOA (*n* = 97) (See Table 1). Genotyping was performed using established procedures (Barret al., 2004; Coyne et al., 2015; Newman et al., 2005). Genotype frequency did not deviate from Hardy–Weinberg equilibrium for DRD4 or 5-HTT, indicating that genetic variation within our subjects was constant. As MAOA is X-Linked, calculations for Hardy-Weinberg equilibrium were only performed on females, for which our sample did not deviate from Hardy-Weinberg equilibrium.

Table 1. Genotype Distributions and Percentage Frequencies

				Total
DRD4 Genotype				
	7R	No 7R		
	19/19.4%	79/80.6%		**98**
5-HTT Genotype				
	l/l	*s*-allele		
	125/65.8%	65/34.2%		**190**
MAOA Genotype				
	5R	6R	7R	
	40/41.2%	25/25.8%	32/33.0%	**97**

Note. DRD4 Genotype: No 7R includes 5R, 5.5R, 6R, 6.5R. 5-HTT Genotype: *l/s* and *s/s* were combined for analyses. MAOA Genotype: 5R and 6R were combined, as per convention (Newman et al., 2005), to form the MAOA-H grouping, while 7R represented the MAOA-L grouping. Subsequent analyses suggested an independent effect for each of the alleles (5R, 6R, 7R). Therefore, subsequent analyses were performed for each allele individually.

DRD4

DRD4 genotypes were determined by amplifying a ~300 bp region on chromosome 14 with forward primer of 5′-GTGGTCTACTCGTCCGTGTG and a reverse primer of 3′-CGTACTCCTCCCCTCCTCTC. Genotyping procedures for DRD4 are described in detail elsewhere (see Coyne et al. (2015)). Briefly, Applied Biosystem's Amplitaq Gold Fast PCR premix was used with an annealing temperature of 64°C for 35 cycles: 95°C, 10 min; 35× (96°C, 3 sec; 64°C, 3 sec; 68°C, 10 sec); 72°C, 10 sec; 4°C, hold. Amplicons were separated by electrophoresis on 4-20% TBE gels at 210V for one hour, and the alleles (5R, 5.5R, 6R, 6.5R, and 7R) were identified by direct visualization following ethidium-bromide staining.

5-HTT

The serotonin transporter gene promoter region (5-HTT) was determined by amplifying from 25 ng of genomic DNA with primers (stpr5, 5′-GGCGTTGCCGCTCTGAATGC; intl, 5′-CAGGGGAGATCCTGGGAGGG) in 15-µL reactions with Platinum™ Taq and the PCR_X Enhancer System kit, according to the manufacturer's protocol (Invitrogen™, Carlsbad, California). Genotyping procedures for 5-HTT are described in detail elsewhere (see Barr et al., 2004). Amplifications were performed on a Perkin Elmer® (Wellesley, Massachusetts) thermocycler (9700) with one cycle at 96°C for 5 min, followed by 30 cycles of 94°C for 15 sec, 60°c for 15 sec, 72°C for 30 sec, and a final 3-min extension at 72°C. Amplicons were separated by electrophoresis on a 10% polyacrylamide gel, and the short (*s*, 388 bp) and long (*l*, 419 bp) alleles of the rh5-HTTLPR were identified by direct visualization after ethidium bromide staining.

MAOA

The monoamine oxidase gene promoter region (MAOA) was determined by using custom primers that flanked the site of interest. Genotyping procedures for MAOA are described in detail elsewhere (see Newman et al. (2005)). Polymerase chain reaction amplification oftarget sequence was carried out, and products were separated by electrophoresis and analyzed by autoradiography for genotype. Primers were derived from a 1.3-kb clone rhMAP-1327 (EMBL-GenBank accession number AJ544234) that was isolated from genomic DNA by polymerase chain reaction (PCR) with primers map1 5'-ATATACGCGTCCCAGGCTGCTCCAGAAAC-3' and map2 5'-ATCTCGAGCTTTGGCTGACACGCTCCTG-3'. Oligonucleotide primers flanking the rhMAOALPR and corresponding to the nucleotide positions -1327 to-1309 (malpr1, 5'-CCCAGGCTGCTCCAGAAAC) and -1103 to-1086 (malpr2, 5'-GACCTGGGAAGTTGTGC) with respect to the translation initiation codon of the rhesus monkey MAOA gene 5' flanking regulatory region were used to generate 206 (5R)-, 224 (6R)-, or 242 (7R)-bp fragments.

Chinese Ancestry

Ancestry was determined by using an extended pedigree to trace each subject's ancestry back to the colony's original founders. Strain type was determined by city and country of origin, as well as the date of birth of the original founders. Monkeys with less than 50% Chinese ancestry varied between 6.25%— 25% Chinese ancestry. Because this low degree of Chinese ancestry would likely have made the effect of Chinese ancestry in this group unclear, only Indian-derived monkeys (*n* = 158) and Chinese-derived monkeys with 50% or greater Chinese ancestry (*n* = 54) were included in the comparisons between strains of the genotypes in question. For the distribution of alleles by strain type, see Table 2.

Table 2. Genotype Distributions and Percentage frequency by Strain Type

	Indian-Derived	Chinese-Derived	Total
DRD4			
No 7R	67/91.8%	12/48.0%	79
7R	6/8.2%	13/52.0%	19
Total	**73**	**25**	**98**
5-HTT			
l/l	102/73.9%	23/44.2%	125
s-allele	36/26.1%	29/55.8%	65
Total	**138**	**52**	**190**
MAOA			
5R	31/47.0%	9/29.0%	40
6R	10/15.1%	15/48.4%	25
7R	25/37.9%	7/22.6%	32
Total	**66**	**31**	**97**

Note. DRD4 Genotype: No 7R includes 5R, 5.5R, 6R, 6.5R.

Data Analysis

To compare DRD4, 5-HTT, and MAOA genotype frequency between the two strains, χ^2 tests of independence were performed, with strain type as the grouping variable, and frequency of the respective genotypes as the outcome variable. Following the established rhesus macaque DRD4 genotype groupings (Coyne et al., 2015), two groups were used in the analyses: subjects which has no copies of the 7R (5R, 5.5R, 6R, and 6.5R) and subjects which had at least one copy of the 7R. Due to low number of subjects homozygous for the *s*-allele of the serotonin transporter ($n = 5$), *s/s* and *l/s* subjects were combined into one group (*s*-allele) for purposes of analyses, as has been done in other studies (Bennett et al., 2002; Schwandt et al., 2010). Because only 1 subject possessed the rare *Xll* genotype, it was excluded from 5-HTT analyses. As MAOA is X-linked (Newman et al., 2005), only males and homozygous females were included in analyses of MAOA genotype. Using the established allele groupings for rhesus monkeys (Karere et al., 2009; Newman et al., 2005), two MAOA genotypes groupings were used: a high activity (5R, 6R) and a low activity (7R) group. Preliminary analyses showed that a grouping by the alleles produced an effect that was independent of the typical genotype groupings; therefore, a separate set of analyses was performed with each of the three alleles (5R, 6R, and 7R) grouped separately, as has been done in other studies (Hunter et al., Manuscript in preparation; Karere et al., 2004). All analyses were conducted in SPSS, version 26 (IBM, 2019).

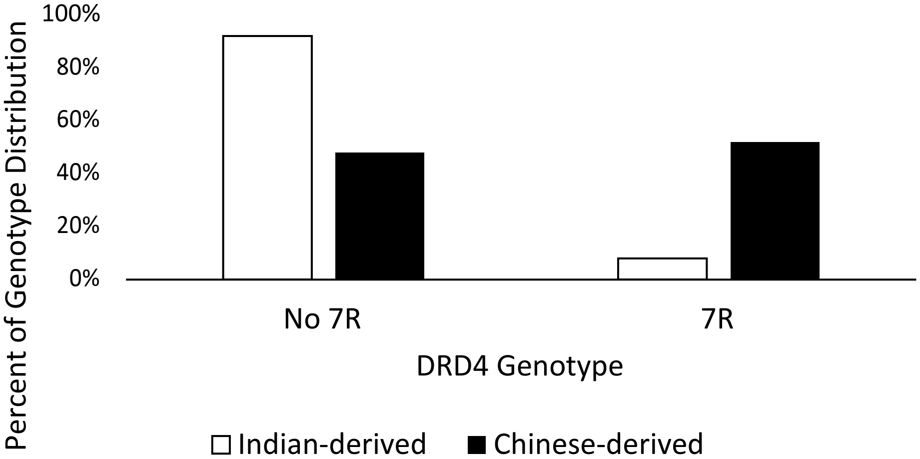
As noted earlier, the colony is outbred; in order to assure that the effects are not due to overall relatedness, each of the genotypes (and additionally, each of the three alleles for MAOA) were dummy coded and analyses were performed to assess if the three genotypes are correlated. Results from these analyses showed no significant between-genotype correlations ($p > .05$), an indication that the effects of the three genotypes are not likely a result of relatedness.

Results

DRD4

There was a significant association between strain and genotype frequency for DRD4, ($\chi^2(1, N = 98) = 22.84, p < .001$), with the Chinese-derived subjects exhibiting a greater frequency of the long allele (7R), when compared to the Indian-derived subjects (see Figure 1).

Figure 1. Association between Strain Type and DRD4 Genotype

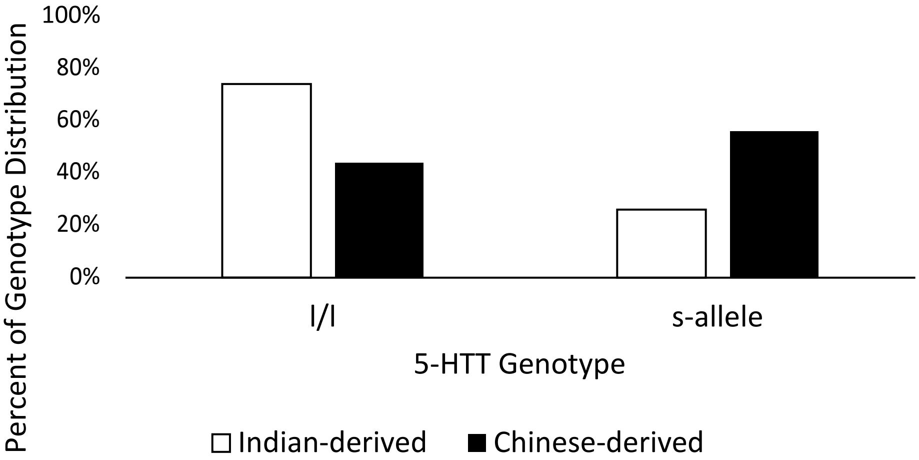


Results from a chi-square test showed a statistically significant association between strain and DRD4 genotype ($\chi^2(1, N = 98) = 22.839, p < .001$), with the Chinese-derived subjects more likely to possess the long allele (7R), when compared to Indian-derived subjects. Bars in black represent Chinese-derived rhesus macaques, while white bars represent rhesus macaques of Indian origin.

5-HTT

There was a significant association between strain and genotype frequency for 5-HTT (χ^2 $(1, N = 190) = 14.79, p < .001$), with the Chinese-derived subjects exhibiting a greater frequency of the *s*-allele, when compared to the Indian-derived subjects (see Figure 2).

Figure 2. Association between Strain Type and 5-HTT Genotype

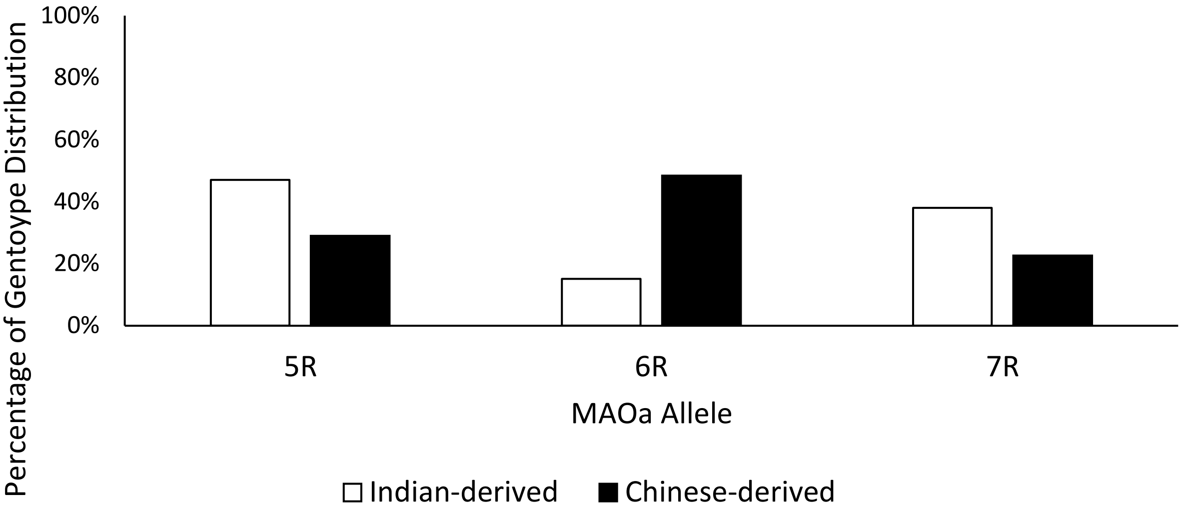


Results from a chi-square showed a statistically significant association between strain and 5-HTT genotype (χ^2 (1, *N* = 190) = 14.785, *p* < .001) with Chinese-derived subjects more likely to possess the *s*-allele, when compared to Indian-derived subjects. Bars in black represent Chinese-derived rhesus macaques, while white bars represent rhesus macaques of Indian origin.

MAOA

Using the conventional genotype allele groupings, there was not a significant association between strain and genotype frequency for MAOA (χ^2 (1, *N* = 97) = 2.23, p = .135), although the frequency of MAOA-L was lower in Chinese-derived subjects than it was in Indian-derived subjects. When the frequency of the three alleles were compared separately, there was a significant association between strain and genotype frequency for MAOA (χ^2 (2, *N* = 97) = 12.18, *p* = .002), with the Chinese-derived subjects exhibiting greater frequency of the 6R allele, when compared to the Indian-derived subjects (see Figure 3).

Figure 3. Association between Strain Type and MAOa Allele



Results from a chi-square test showed a statistically significant association between strain and MAOA allele (χ^2 (2, *N* = 97) = 12.182, p = .002), with the Chinese-derived subjects more likely to possess the 6R allele, when compared to Indian-derived subjects. Bars in black represent Chinese-derived rhesus macaques, while white bars represent rhesus macaques of Indian origin.

Discussion

Rhesus macaques have experienced several periods of broad geographic expansion (Xue et al., 2016), expanding within and beyond forested habitats into a variety of environments. Consistent with the study's hypotheses, the descendants of groups that occupy more high-demand environments exhibited a greater frequency of the DRD4-7R and the 5-HTT *s*-allele, when compared to the descendants of subjects that are found in more stable, productive environments (See Figures 1 and 2, respectively). Using the conventional high-activity-/low-activity- MAOA genotypes (Karere et al., 2009; Newman et al., 2005), analyses failed to detect differences between the two geographic groups in the frequency of the MAOA-H genotype. When MAOA alleles were compared separately, however, a significant difference emerged between Chinese- and Indian-derived subjects, with Chinese-derived subjects exhibiting a greater frequency of one of the high-activity alleles, when compared to their Indian-derived peers. Genetically-mediated traits favoring expansion into those novel environments, such as novelty seeking, impulsivity, and aggression may have played a role in the Chinese-derived subjects' expansion to new territory, and competitive ability within those new environments.

The DRD4-7R genotype is frequently associated with novelty-seeking and risk taking in humans (Bailey et al., 2007; Carpenter et al., 2011; Chen et al., 1999; Dulawa et al., 1999; Ebstein et al., 1996; Fidler et al., 2007; Hejjas et al., 2007; Korsten et al., 2010; Momozawa et al., 2005). Research in other animals indicate that these traits are implicated in the radiation of species into unfamiliar environments (Brodin et al., 2012; Liebl & Martin, 2014; Martin & Fitzgerald, 2005; Møller & Garamszegi, 2012; Mueller et al., 2014; Riyahi et al., 2016). Groups of humans whose ancestors radiated into unfamiliar environments farther from Africa possess a higher frequency of the DRD4-7R polymorphism than groups that exhibited less distant radiations (Chang et al., 1996; Wang et al., 2004). For example, Native Americans, whose ancestors nomadically crossed into the Americas from Asia via the Bering land bridge, have the highest frequency of the DRD4-7R found among humans (Chang et al., 1996; Chen et al., 1999; Tovo-Rodrigues et al., 2010), and this group occupies territories ranging from tundra to temperate forests, prairies, deserts, and tropical jungle. Among nomads in Africa, individuals possessing the DRD4-7R exhibit improved nutritional state over members of their group that lack this genotype (Eisenberg et al., 2008). It has been implied that this may be an outcome of exploiting novel opportunities, including territories and food sources. As with humans (Ebstein et al., 1996), studies in both vervet monkeys (*Chlorocebus pygerythrus*) (Bailey et al., 2007) and rhesus macaques (Coyne et al., 2015) indicate that variation in the DRD4 is associated with novelty-seeking, an important component of a bold and high risk-taking behavioral response that may have been adaptive to groups of rhesus macaques that colonized unfamiliar and challenging territories in China.

Rhesus macaques are widely considered to be one of the most aggressive representatives of the genus *Macaca* (Wendland, Lesch, et al., 2006) and aggression can be adaptive in facilitating the geographic expansion of aggressive species (Duckworth, 2008; Duckworth & Badyaev, 2007; Pintor et al., 2008; žganec et al., 2014), enabling those species to outcompete less aggressive resident species for desired territories (Dow, 2016; Duckworth & Badyaev, 2007; Kumar et al., 2011; Polo-Cavia et al., 2010; Weis, 2010). One of the most replicated findings in biological psychiatry and psychology is the link between low or impaired central serotonergic functioning and impulsive aggression (Brown et al., 1979; Higley et al., 1996; Higley et al., 1992; Howell et al., 2007; Kruesi et al., 1990; Lidberg et al., 1985; Linnoila et al., 1983; Virkkunen et al., 1995; Virkkunen et al., 1987). Studies show that the *s*-allele of the 5-HTT is associated with lower or impaired CNS serotonergic functioning (Bennett et al., 2002; Reist et al., 2001). Impulsivity and aggressiveness, which are more frequently exhibited by subjects that possess the *s*-allele (Aluja et al., 2009; Retz et al., 2004; Suomi, 2004), may be beneficial for groups facing challenging and dangerous environments, and it appears that, as with humans, populations of rhesus macaques whose ancestors entered less abundant environments also exhibit higher frequencies of the *s*-allele.

Some authors suggest that rather than being associated with one specific trait, the *s*-allele may confer behavioral plasticity, in general, increasing the capacity to adapt to different environmental demands (Shattuck et al., 2014). It is of note that the *s*-allele emerged independently in humans and rhesus monkeys (Lesch et al., 1997; Shattuck et al., 2014), two species of primates characterized by their expansive geographic ranges and behavioral flexibility.

While speculative, behavioral sensitivity and plasticity may have also allowed for more varied responses to the environmental demands the ancestors of Chinese-derived rhesus macaques encountered as they occupied their current geographic range.

When the Chinese and Indian-derived rhesus macaques were compared using the traditional MAOA-H grouping (5R/6R), there were no statistically significant differences in the frequency of MAOA-L and MAOA-H genotypes between the two strains. When examining each allele separately, however, the high-activity 6R allele was more frequent in Chinese-derived subjects that it was in Indian-derived subjects. Other studies in nonhuman primates suggest differences in both behavior (Karere et al., 2004) and monoamine metabolite concentrations (Hunter et al., Manuscript in preparation) between subjects that possess the 5R and 6R allele. While those alleles are frequently grouped together in studies assessing the MAOA-H genotype in rhesus monkeys, there may be differences between the 5R and 6R that are at variance with the conventional MAOA genotype groupings for this species. Studies from our laboratory show that rhesus macaque infants that possess the 5R rarely differ from those that possess the 7R in concentrations of the metabolites of serotonin, dopamine, and norepinephrine, and that in terms of monoamine metabolite degradation, it is those with the 6R that exhibit higher activity leading to higher monoamine metabolites (Hunter et al., Manuscript in preparation). While the extent to which these differences in monoamine metabolite degradation correlate to aggressive behavior remains unclear, future research may benefit from applying the approach of the current study and evaluating the effects of each allele separately in rhesus monkeys.

One cannot rule out genetic drift and neutral selection as mediators of genotype frequency differences observed by the two populations of rhesus macaque. It is well-established that Indian-derived rhesus macaques exhibit less heterozygosity than Chinese-derived rhesus macaques, suggesting that the Indian-derived population experienced a genetic bottleneck (Ferguson & Smith, 2015; Hernandez et al., 2007; Melnick et al., 1993; Satkoski et al., 2008; Smith et al., 2006; Xie et al., 2012; Xue et al., 2016). Moreover, Chinese-derived rhesus macaques display a substantially larger wild population than the Indian-derived rhesus macaques (Liu et al., 2018), which may further complicate determinations of the potential role of neutral selection over genetic drift. While we were unable to assess the genetically-mediated behavior traits associated with the candidate genes studied, previous research abounds in support of the association between the candidate genes examined in this study, and their proposed behavioral traits in nonhuman primates. It is likewise possible that components of this behavioral repertoire may have also been selected for in the human groups that radiated out of Africa, for the 5HTT and MAOa genotypes, although to the authors' knowledge, this has not been previously assessed.

The current study utilizes a natural model of two strains of the same species that have adapted to very different environments to assess whether the frequencies of the genotypes associated with these traits are more frequent in subjects that have come to occupy more distal, varied, and demanding environments. Together the increased frequency of the genotypes of interest to the current study may have provided traits that allowed the Chinese-derived subject to better exploit novel resources and challenging environments and perhaps to aggressively acquire and defend new territory. This knowledge regarding genetic characteristics of the two populations may provide a scaffold for future studies evaluating behavioral and temperament differences between the two rhesus macaque strains. The findings of this study present tantalizing parallels with what is observed with the human Out of Africa expansion, and suggest that future research using rhesus macaques to model mankind's expansion out of Africa may prove informative in delineating factors involved in our species spread and adaptation to novel environments.

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