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Male Reproductive Timing in Rhesus Macaques Is Influenced by the 5HTTLPR Promoter Polymorphism of the Serotonin Transporter Gene[1]

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ABSTRACT

The 5HTTLPR polymorphism in the promoter region of the human serotonin transporter (*SLC6A4*) gene is known to be associated with various stress-related psychological and psychiatric phenomena. We observed that a similar diallelic polymorphism in the orthologous gene of rhesus macaques (*Macaca mulatta*) was related to the reproductive life history of 580 males residing in the free-ranging colony of Cayo Santiago, Puerto Rico, between 1985 and 1998. At first glance, the polymorphism appeared to be selectively neutral because no difference in total reproductive output was noted between males of different 5HTTLPR genotypes. However, whereas heterozygotes were significantly more reproductive than homozygotes at intermediate age (10–13 yr), the opposite held true before and after this period (n = 682 offspring; randomization $P = 0.014$). This association, which explains approximately 7% of the observed variation in sire age, most likely reflects different natal dispersal patterns and represents the first reported instance of a genetic influence on reproductive timing in mammals.

behavior, male reproductive timing, male sexual function, neurotransmitters, rhesus macaques, serotonin transporter

INTRODUCTION

Several studies in humans and nonhuman primates have linked brain serotonin activity to impulsive behavior, risk-taking, suicide, and aggression [1–7]. Individuals with low levels of serotonin metabolite 5-hydroxyindoleacetic acid (CSF 5-HIAA) generally exhibit a trend toward aggressive and impulsive behavior, whereas high levels of CSF 5-HIAA are associated with reduced aggression. In humans, expression of the serotonin transporter gene, *SLC6A4*, has been shown to be influenced by a variable number of tandem repeat polymorphisms (5HTTLPR) in the promoter region of the gene [8]. Analogous variants have been identified in the *SLC6A4* orthologues of several simian primates, suggesting that the polymorphism arose in the genome of a common ancestor some 40 million years ago [9]. Of the two major 5HTTLPR alleles, S (*short*) and L (*long*), the S variant was found to reduce transcriptional efficiency in cultured human lymphoblast cells [8]. The same study also revealed an association between the LS and SS genotype, respectively, and both anxiety and depression-related personality traits in humans, prompting a large number of follow-up investigations of similar type [10–16].

Dispersal from the natal group is a common, albeit highly variable, behavioral pattern in primates. Depending on the species considered, either males or females, or both genders, may migrate. In rhesus macaques (*Macaca mulatta*), only males transfer, while females remain in their natal groups throughout their lives [17]. Natal dispersal entails the loss of social status and an increase in mortality and stress. However, the causes of this behavior have remained enigmatic. At a socioecological level, both inbreeding [18] and male-male competition [19] have been invoked. Young males might thus be willing to mate with any female, but if most females either refuse to mate or cannot be accessed for sexual consort, then males would be rewarded in terms of reproductive opportunities by looking to a different troop.

Evidence for a strong role for serotonin function in mediating early migration patterns in male rhesus macaques came from the observation that the age at natal dispersal is directly related to the cerebrospinal concentration of CSF 5-HIAA [20, 21]. Because the 5HTTLPR polymorphism in the rhesus *SLC6A4* homologue also influences anxiety and the response to stress and adversity [22–24], an association between the polymorphism and early male migration patterns is highly plausible. Indeed, we have previously demonstrated that among the free-ranging rhesus macaques of Cayo Santiago, Puerto Rico, SS homozygous males leave their natal groups 6 to 15 mo earlier than carriers of the L allele [25].

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Natal dispersal on Cayo Santiago is associated with a 6% mortality rate [26]. However, because the island is predator-free, and colony members forage on both the natural vegetation and on artificially enhanced food resources, the most common reason for failing to survive male dispersal is likely to be stress-related physiological impairment of the immune system. Such an impairment could either compromise the ability to cope with wounds received while attempting troop entry, or weaken the animal and therefore diminish his prospects of foraging successfully. We initially speculated that dispersal at an intermediate age would therefore confer a subtle reproductive advantage to heterozygous males, but no notable difference in offspring number was observed between males of different 5HTTLPR genotype [25]. Now, an in-depth analysis of the reproductive life history of individual male monkeys provides evidence that 5HTTLPR is instead associated with a significantly different timing in offspring production.

MATERIALS AND METHODS

Study Population and Genotyping

Genotyping of the rhesus 5HTTLPR analogue was performed as previously described [25]. All animals analyzed in the present study were from the free-ranging colony of rhesus macaques residing on Cayo Santiago, Puerto Rico, which is maintained by the Caribbean Primate Research Center, University of Puerto Rico Medical Sciences Campus [27]. Animals in the colony are subject to regular census, and demographic events such as birth, death, and migration are generally noticed within 2 days. Male natal dispersal on Cayo Santiago has been operationally defined as not returning to the natal group for 30 consecutive days [26]. In our study, we have included all 682 colony infants, born between 1985 and 1998, for whom paternity could be determined by means of molecular genetic testing [28]. All males aged 5 to 19 yr who lived in the colony at any time during the 6 mo before a given birth, and for whom a blood sample was available for genotyping, were considered possible sires of the respective infant. Paternity was determined using 15 microsatellites [28] with $\log_{10}$-likelihood ratios (LR) for paternity vs. nonrelatedness calculated as previously described [29]. Paternity of a given individual was regarded as established when the putative sire had an LR in favor of paternity that was greater than two (corresponding to a standardized paternity probability of 99%), and at least one unit greater than the LR of any other potential sire. When applying these criteria, paternity could be ascertained for 71% of the infants born during the study period. All animals of this study were sampled not specifically for this study, but during the regular annual medical checkup performed on all animals in the Cayo Santiago facility.

Statistical Analysis

The average lifetime reproductive output of males with a given 5HTTLPR genotype was estimated as the number of offspring sired by such males, divided by the genotype-specific sum of all lifetime periods of potential sires overlapping with the study period (*sire years*). The expected offspring number for males of a given age and genotype, assuming no association between reproductive timing and genotype, was calculated as the total offspring number for the respective age group, multiplied by the relative proportion of males with the particular genotype in question among all potential sires of that age. Differences between the reproductive timing of males with different genotypes were assessed for statistical significance by applying a Kolmogorov-Smirnov test to the respective sire-age distributions. Valid *P* values were obtained by randomization (10 000 repetitions), each time shuffling the genotypes of all males ever considered as a potential sire. The strength of the association between dichotomized sire genotype and age was quantified for the 682 infants using the Jolayemi τ statistic [30], a measure of concordance that ranges between zero (no association) and unity (perfect concordance). A major advantage of τ over other association measures is the interpretability of τ^2 as a coefficient of determination [30]. Because the definition of the age and genotype categories was based on post hoc considerations, no attempt was made to assess the statistical significance of τ. The association between male age at first dispersal and male age at death was analyzed using life table (Kaplan-Meier product limit) methodology as implemented in the LIFETEST procedure of SAS/STAT Version 8.02 (SAS Institute Inc., Cary NC). Because both variables can potentially be censored, the analysis had to be carried out twice, each time excluding males for which a given item (i.e., either dispersal or death) had not actually been observed.

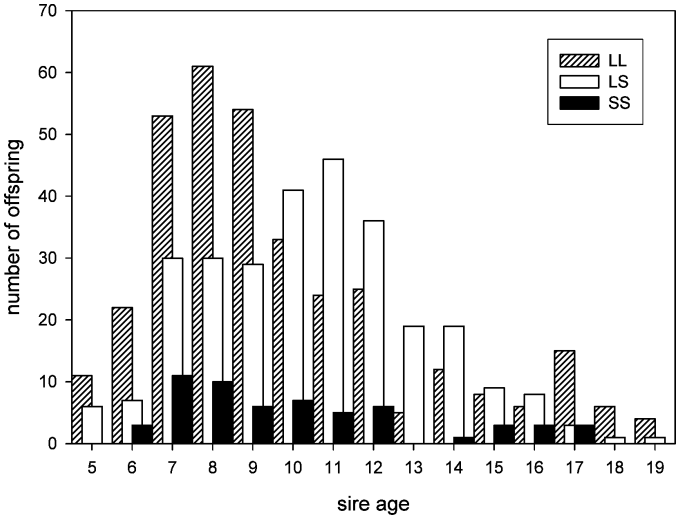

FIG. 1. Number of offspring sired by Cayo Santiago male rhesus macaques of different ages.

RESULTS

Distribution of 5HTTLPR Genotypes

A total of 580 males of known 5HTTLPR genotype were considered as a potential sire at least once during the study period. Of these, 279 were LL homozygous, 243 were LS heterozygous, and 58 were SS homozygous. While the exact age at dispersal was recorded for 284 males, the same was true for the age at death of 106 males. In any case, neither of the two investigations revealed any significant association between the age at death and at dispersal (log-rank chi-square = 0.125 for known age at death, chi-square = 0.030 for known age at dispersal, 1 *df*, $P > 0.5$). The 682 infants analyzed were born to 210 different females, among which genotype counts were 99, 87, and 24, for LL, LS, and SS respectively. There was thus no notable parental sex difference in terms of genotype frequencies (chi-square = 0.341, 2 *df*, $P = 0.843$). Although the number of potential sires with known genotype varied between 88 in 1985 and 406 in 1998, no significant variation in allele frequency was observed over time, and both male and female genotype frequencies were found, consistently, to be in Hardy-Weinberg equilibrium (data not shown).

Male Reproductive Success and 5HTTLPR Genotype

During the study period, LS heterozygotes were found to have sired 285 offspring, while LL and SS homozygotes sired 339 and 58 offspring, respectively. When these figures were divided by the respective total number of sire years, the overall reproductive output of the three genotypes was found to be virtually identical (LL, 339/1731 = 0.196; LS, 285/1498 = 0.190; SS, 58/312 = 0.186). However, while heterozygous males experienced an increasing rate of reproduction until the age of 11 yr, followed by a constant decline thereafter, both homozygous genotypes showed a pronounced reproductive mode at 7–8 yr, and a second mode around 16–17 yr of age (Fig. 1). When assessed by a randomized Kolmogorov-Smirnov test, the difference between the two homozygous genotypes was found to be neg-

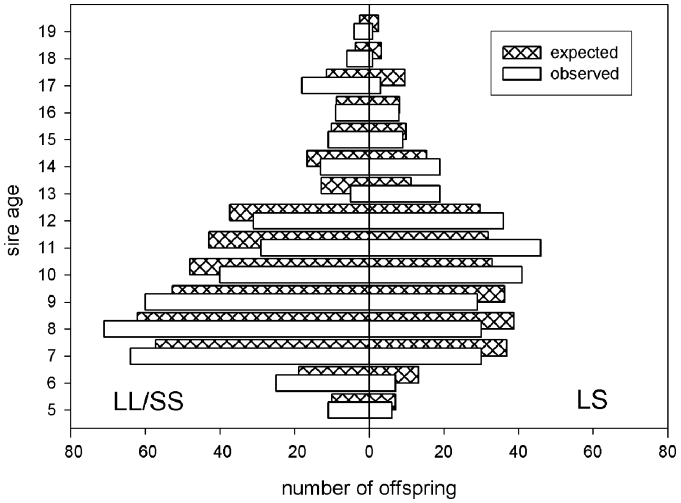

FIG. 2. Observed and expected number of offspring of LL/SS homozygous males (left) and LS heterozygous males (right), assuming no association between reproductive timing and 5HTTLPR genotype.

ligible ($P = 0.951$), while their combined genotype-specific lifetime reproductive profile differed significantly from that of heterozygotes (randomization $P = 0.014$). A comparison between the observed and expected number of offspring, based on the number of potential sires in each age group, also highlighted that heterozygotes overperformed between the age of 10 and 14 yr, while homozygotes underperformed during the same period of life (Fig. 2). Based on this classification, the number of offspring sired by males of a given genotype and age could be arranged in a 2×2 table (Table 1). As was to be expected, sire genotype and sire age turned out to be slightly to moderately associated with one another ($\tau = 0.269$). No comparable genotypic differences in reproductive timing were observed among the female rhesus macaques on Cayo Santiago (data not shown).

Male Age at First Reproduction and Natal Dispersal

The mean age at first reproduction of successful LL males (6.98 ± 2.76 yr; n = 99) and SS males (6.92 ± 2.27 yr; n = 16; Student t = 0.08, two-sided $P > 0.5$) was found to be virtually identical. Successful heterozygotes (n = 72) first reproduced at 7.22 ± 2.23 yr of age, but the difference between homozygous and heterozygous genotypes was not statistically significant (t = 0.63). In contrast, upon stratification by dispersal age, males who emigrated at an intermediate age of 5 yr were found to have produced their first offspring significantly later (age 7.95 ± 2.80 yr; n = 45) than those who emigrated at 4 yr of age (6.78 ± 2.45 yr; n = 56; t = 2.24, two-sided $P < 0.05$) or at 6 yr of age (6.55 ± 1.60 yr; n = 20; t = 2.08, two-sided $P < 0.05$).

Male Breeding Life Span

No observational data on individual males were available in the present study that would have allowed breeding life spans to be assessed and related to male 5HTTLPR genotypes. Furthermore, reproductive success is known to be very unevenly distributed among male rhesus macaques on Cayo Santiago [31], which implies that the database for such an analysis would have naturally been small. In any case, when the time difference (Δ_t) between the first and last (recorded) reproduction was analyzed for those 30 males who 1) had at least two offspring during the study period and 2) lived at least until the median male age of death on Cayo Santiago (18.7 yr), a notable difference between heterozygotes and homozygotes was observed. While the average Δ_t was 6.9 yr among LS males (n = 13), it was 10.6 yr in LL males (n = 14) and 10.0 yr in SS males (n = 3). When Δ_t values for homozygotes and heterozygotes were compared using a Wilcoxon test, the observed mean difference of 3.6 yr was found to be statistically significant (chi-square = 3.953, 1 *df*, $P = 0.047$).

TABLE 1. Number of offspring classified by sire genotype and sire age.

Sire age class (yr)	LL, SS	LS	Total
5–9, 15–19	279	124	403
10–14	118	161	279
Total	397	285	682

DISCUSSION

In virtually all higher organisms, the timing and duration of reproductive activity are highly variable at both the individual and population levels. Understanding the basis of this variation is fundamental to comprehending the ecology and behavior of a particular species [32]. Theoretical models predict that natural selection would cause the reproductive lifespan of males to increase in environments characterized by high survival and low competitive costs [32]. As yet, however, the potential genetic targets for such changes in selective pressure are broadly unknown. For example, although juvenile hormone (JH) has been shown to control the switch from reproductive plasticity to reproductive inflexibility in lubber grasshoppers (*Romalea microptera*), the respective experiments employed dietary variation to induce different JH levels rather than employing naturally occurring, or artificially induced, genetic variants [33]. Similarly, differences in reproductive timing observed in the field between urban and forest-dwelling European blackbirds (*Turdus merula*) did not persist under laboratory conditions, thus indicating that these differences were largely a result of phenotypic flexibility [34]. Although urban males were found to initiate the secretion of plasma LH earlier than forest males, and although plasma LH concentration and follicle size declined earlier in urban females than in forest females, the genetic differences invoked were not elucidated any further.

Our study has revealed, for the first time, that reproductive timing in mammals may be influenced by genetic factors. Male rhesus macaques who are homozygous for the diallelic 5HTTLPR polymorphism in the serotonin transporter gene were found to be reproductively more successful during early and late adulthood than their heterozygous counterparts, who reproduced mainly at an intermediate age. The polymorphism in question is known to influence the response to stressful events [35] and to alter the functional response of the serotonin system in humans [36]. In rhesus macaques, 5HTTLPR interacts with the early experiences of monkeys to influence the function of serotonin in their central nervous systems [37]. While animals with deleterious early rearing experiences are characterized by genotype-dependent cerebrospinal CSF 5-HIAA concentrations, monkeys reared normally are not [22]. Similar studies on the response of ACTH to stress have revealed that higher levels of ACTH are associated with carriership of the S allele in male macaques, but that the effect on females is limited to those with an early experience of adversity [23].

Finally, infant and juvenile SS monkeys were found to be behaviorally inhibited and engaged in more fearful behaviors under controlled experimental conditions than their LS and LL counterparts [24].

With breeding being an essential component of normal animal behavior, the above findings suggest that the observed variation in reproductive timing of male rhesus macaques may be a direct result of variation in serotonin transporter gene expression. As yet, however, there are no reports in the scientific literature of a possible causal relationship between serotonin transporter function and reproductive behavior, neither in humans nor in any other species. Instead, we have previously demonstrated that 5HTTLPR in rhesus macaques is associated with the age of male natal dispersal [25]. Although troop dispersal among male monkeys can also be considered a stressful life history event, our data nevertheless suggest that the observed association between 5HTTLPR genotype and male reproductive timing is not primarily due to an increased or decreased willingness to engage in risky behavior during that particular period of life. Thus, the age at male natal dispersal was not found to be strongly associated with overall life expectancy, which means that the observed difference in reproductive timing could not simply be attributed to differential mortality. Furthermore, the mean age at first reproduction of LL and SS homozygous males was found to be the same, despite a pronounced tendency of the latter to leave their natal groups much earlier. This notwithstanding, age at male natal dispersal may still have represented a critical determinant of genotype-specific reproductive opportunities, at least in early adulthood. While SS homozygotes emigrate early, causing them to initiate reproduction mainly in non-natal groups, LL homozygotes disperse late and are therefore likely to first reproduce in their natal groups. Heterozygotes, in contrast, pursue an intermediate tactic that would delay their reproductive onset for some time. This dichotomy implies that at least some of the influence of 5HTTLPR on male reproductive timing in our study was indirect in nature and resulted from the codominant effect of the polymorphism on male migratory behavior [20].

Formally, the 5HTTLPR genotype was found to be slightly to moderately associated with sire age ($\tau = 0.269$). When the square of the Jolayemi τ is interpreted as an R^2-type statistic [30], this implies that some 7% of the observed variation in male reproductive timing is explicable in terms of an indirect, dispersal-mediated effect of individual serotonin transporter protein level ($\tau^2 = 0.072$). It is therefore likely that other, hitherto unknown genetic variants have exerted an influence on male reproductive timing in our study group as well. However, such a causal link would be difficult to prove unless strong and plausible candidate genes were available for testing. First, reproductive timing represents a quantitative trait that is difficult to integrate in a single parameter amenable to formal genetic linkage or association analysis, especially considering the low average number of offspring produced by most males on Cayo Santiago. Second, the localization of causative genes using anonymous markers under the linkage paradigm would require data on reproductive timing from multigeneration families, which are simply not available even for the well-characterized population analyzed here. Finally, at least in humans, the heritability of behavioral traits is usually comparatively low (0.4 to 0.6 [38]), and the complexity and diversity of the underlying genetic mechanisms is unknown beforehand. Furthermore, studies on insects, reptiles, and birds [33, 34, 39] have highlighted that even subconscious reproductive processes are heavily dependent on environmental factors, suggesting that this is even more likely to be the case for tactics consciously pursued by primates.

That no difference in reproductive timing was observed among females is not surprising, because female macaques stay in their natal groups throughout their lives. They do not therefore represent a target for dispersal-associated factors that influence reproductive behavior. Nevertheless, in a number of nonhuman primate species, including rhesus macaques, the lifetime reproductive success of females has been found to be a function of their breeding lifespan rather than mere age at onset of reproduction [40]. If the same were true for the males in our study, then we would have expected their breeding life span to be as independent of their 5HTTLPR genotype as was their total reproductive output. However, the time difference between first and last reproduction of successful heterozygotes and successful homozygotes was striking. Although this time difference represented only a surrogate measure of actual breeding life span, it appears likely that the genotype-dependent difference in male reproductive timing observed on Cayo Santiago is, at least to some extent, mediated by the length of time that males stay sexually active.

While overdominant selection (*heterozygote advantage*) is usually invoked to explain how a genetic polymorphism may persist in a population, the 5HTTLPR-associated tactics of male rhesus macaques in our study group resulted in comparable reproductive output. Therefore, the observed dichotomy in reproductive timing suggests a hitherto unrecognized evolutionary mechanism, reminiscent of *overcompensation* [41], by which a genetic polymorphism is maintained through the provision of genotype-specific reproductive niches. If carriers of different genotypes reproduce at different ages, the host population is no longer panmictic. Instead, it attains a level of temporal stratification that reduces the gametic sampling variance and thereby delays allele fixation through drift or a (net) selective advantage [42]. In its most extreme form, this mechanism could increase the mean sojourn time of an otherwise neutral allele by up to 33%, depending on the overlap in reproductive activity. Although a delay of this magnitude may appear small at first glance, it could have been critical for the evolutionary preservation of 5HTTLPR among rhesus macaques, especially during the dispersal of small founder populations when more subtle and yet unknown selective advantages would have been dominated by drift.

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