ORIGINAL RESEARCH

Genetic Heterozygosity and Sociality in a Primate Species

Marie J. E. Charpentier · Franck Prugnolle · Olivier Gimenez · Anja Widdig

Abstract The relationship between an individual's genotype and its phenotype is a central issue in biology, but one that is largely unexplored for the important phenotype of complex social behavior. Here we examine the relationship between heterozygosity and social behavior among unrelated adult female rhesus macaques living on the island of Cayo Santiago (Puerto Rico). We show that female macaques with lower mean neutral heterozygosity were discriminated against by their unrelated conspecifics: less heterozygous females received aggressive behavior at higher rates and received affiliation at lower rates than more heterozygous females. We demonstrate that these results are likely due to local genomic effects associated with particular microsatellite loci. Our study suggests that genetic characteristics can impact the way an individual experiences its social environment and that female macaques that are homozygous at two microsatellite loci appear to be less attractive social partners based on grooming and aggression received by unrelated conspecifics.

Edited by Yong-Kyu Kim.

Marie J. E. Charpentier and Anja Widdig contributed equally to this work.

M. J. E. Charpentier (✉)
Department of Biology, Duke University, Science Drive, Biological Bldg 020, PO 90338, Durham, NC 27708, USA
e-mail: mariecharp@yahoo.fr

M. J. E. Charpentier · O. Gimenez
Centre d'Ecologie Fonctionnelle et Evolutive, CNRS, Montpellier, France

F. Prugnolle
Génétique et Evolution des Maladies Infectieuses, IRD-CNRS, Montpellier Cedex 05, France

O. Gimenez
Centre for Research into Ecological and Environmental Modelling, University of St Andrews, St Andrews, Scotland

A. Widdig
Department of Primatology, Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany

A. Widdig
Caribbean Primate Research Center, Sabana Seca, PR, USA

Genetic heterozygosity has been associated with a range of fitness-related phenotypes in a variety of organisms (see for review Crnokrak and Roff 1999; Keller and Waller 2002). These phenotypes have included survival (Coulson et al. 1998), reproduction (Amos et al. 2001; Charpentier et al. 2005), disease resistance (Coltman et al. 1999), disease susceptibility (Acevedo-Whitehouse 2003), as well as male's secondary sexual traits (Müller and Ward 1995; Aparicio et al. 2001). Homozygous individuals could be physically weaker or in poorer condition, either because of inbreeding depression or because homozygosity at key loci can reduce fitness. To illustrate the latter, some studies on vertebrates have demonstrated that heterozygous individuals at genes from the Major Histocompatibility Complex (MHC) better resist pathogens (Carrington et al. 1999;

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Penn et al. 2002). Furthermore, both Trefilov et al. (2000) and Krawczak et al. (2005) found some evidence of heterozygote advantages at the orthologous gene of the human serotonin transporter gene (SLC6A4) in rhesus macaques (*Macaca mulatta*) in the form of intermediate age at dispersal in heterozygous males and higher reproductive success in heterozygous males who are in their prime (respectively).

Even though studies on the effect of genetic heterozygosity on a range of fitness-related traits are numerous, its influence on social behavior has been given little consideration. There is however evidence that both aggressive behaviors and competitive abilities are influenced by levels of overall inbreeding in mice (*Mus musculus*, Barnard and Fitzsimons 1989; Eklund 1996; Meagher et al. 2000) and drosophila (*Drosophila melanogaster*, Latter and Robertson 1962; Latter and Sved 1994). Genetic heterozygosity alone has been also shown to influence social behavior in salmons (*Salmo salar*), where highly heterozygous individuals initiate more costly aggressive behaviors than more homozygous individuals, increasing their competitive ability (Tiira et al. 2003). Following this study, we hypothesized in a social primate, that homozygous individuals are less socially involved than heterozygous individuals. We first speculate that these homozygous individuals could be less involved in the social life within their group, because they just cannot display as many costly behaviors, such as aggressiveness, as fitter individuals. Second, if homozygous individuals are physically weaker, they could also constitute less preferred social partners, because their conspecifics will not enjoy fitness advantages to interact with them. Indeed, if homozygous individuals are less able to display defensive behaviors and/or are less prone to form coalitions, they could just represent less attractive social partners. In the same way, more homozygous individuals could also be more susceptible to pathogens, as observed in sea lions (*Zalophus californianus*, Acevedo-Whitehouse 2003), and parasitized individuals could act as effective reservoirs of infectious agents and could therefore pose a risk to their congeners, which in turns could socially avoid them (e.g., Kiesecker et al. 1999). These two predictions are not necessarily mutually exclusive.

Our goal was to examine the relationship between multilocus heterozygosity and multiple complex social behaviors between non-kin in a highly social primate. For the purpose of our study, we studied the well-known rhesus macaque population living on the island of Cayo Santiago (Puerto Rico). We hypothesized that more homozygous individuals would exhibit social deficits, either because they are less able to display costly behaviors or because they constitute less attractive social partners.

Methods

Behavioral observations

All individuals present in the island of Cayo Santiago, a 15.2 ha island off the coast of Puerto Rico, are direct descendants of 400 animals captured in India in 1938 (Rawlins and Kessler 1986). This study focused on 51 of 91 female rhesus macaques in group R, aged from one to nine years old at the beginning of the study. Females >9 years old ($N = 40$) were excluded from data collection because we lacked paternity information for them which was the focus of the original study (Widdig et al. 2001, 2002). The fact that we did not consider older females could have potentially influenced our findings if the effects of heterozygosity differ with age, beginning at ages >9 years. While we cannot rule out this hypothesis, combined behavior and genetic data are not yet available for females older than 9 years.

A total of 958 h of focal data (Altmann 1974) were collected on these females between May and December 1997, using 20 min focal samples. Analyses were limited to non-physical aggression (i.e., threats and other gestures that did not entail physical contact between opponents, as data on physical aggression were too limited) and three types of affiliative activity (i.e., grooming, approaches, and occurrence of proximity—5 m radius—between two individuals) that occurred during a focal observation (Widdig et al. 2001; 2002). All behaviors were analyzed as bouts, i.e., the occurrence of behaviors rather than time-periods (see Table 1 for details on the studied behaviors). We indicated whether the focal female initiated or received each behavior (except in the case of proximity where no such differentiation could be made). We further restricted our analyses to non-kin dyads ($N = 1848$) because considering related dyads was problematic. Because our study population is free-ranging and provisioned more kin share

Table 1 Information on the seven studied behaviors across all 51 studied females

Social behavior	Mean	s.e.m.	Range
Aggression initiated	0.006	0.000	0–0.184
Aggression received	0.005	0.001	0–0.414
Initiated grooming	0.007	0.001	0–0.879
Received grooming	0.006	0.001	0–0.776
Initiated approach	0.117	0.004	0–3.931
Received approach	0.135	0.004	0–1.653
Proximity	0.007	0.009	0–4.086

Values represent the mean, s.e.m. and the range of the recorded numbers of bouts per hour, initiated and received by the focal females interacting with their non-kin

the same social group than do in the wild. Therefore, we decided to restrict our analyses to non-kin dyads to avoid potential biases. The 51 studied females belonged to three different matrilines and had between 18 and 79 unrelated females in the group (mean ± s.e.m.: 36.24 ± 2.93).

Genetic analysis

All 51 focal females involved in this study were genotyped at 13 microsatellite loci (Nürnberg et al. 1998; Widdig et al. 2001). Mean heterozygosity per female was calculated as the number of heterozygous loci divided by 13 (mean ± s.e.m.: 0.73 ± 0.02, range: 0.38–0.92; and see Table 2). Pairs of females were considered unrelated ($r \sim 0.00$) when they were (a) born into different matrilines (with matrilineal relationships traced back to 1956), and (b) paternally unrelated (i.e., they were neither paternal half-siblings nor descendants of paternal half-siblings). Paternal kinship was assessed by genotyping all group members, including all potential sires (Nürnberg et al. 1998; Widdig et al. 2001), but paternity was only known for a maximum of three generations.

Genomewide inbreeding or local effects?

Heterozygosity will affect phenotypes either because it reflects genome-wide inbreeding, or because one or more microsatellite loci are physically linked to functional loci. If heterozygosity reflects genome-wide inbreeding, then more homozygous individuals should be uniformly homozygous across all tested markers (Balloux et al. 2004). We randomly generated two data subsets from the single data set of genotypes on the entire population of macaques genotyped at 13 loci ($N = 566$ individuals). Each data subset contained six or seven randomly chosen

Table 2 Mean heterozygosity per locus and s.e.m

Locus	Mean heterozygosity	s.e.m.
D2S367	0.706	0.064
D8S601	0.745	0.062
D20S206	0.784	0.058
D6S493	0.667	0.067
D6S474	0.725	0.063
D20S476	0.627	0.068
D12S66	0.745	0.062
D12S67	0.922	0.038
D14S255	0.627	0.068
D5S820	0.667	0.067
D5S1470	0.804	0.056
D6S266	0.804	0.056
D8S271	0.706	0.064

microsatellite loci from the full set of 13 analyzed loci. We examined the correlation between individual heterozygosity measures in the two data subsets, and then repeated the procedure (generating two data subsets and examining the correlation) 100 times using SPLUS 2000. A significantly positive value for the mean of the 100 'heterozygosity-heterozygosity correlations' would indicate that heterozygous individuals tend to be uniformly heterozygous across all loci. Therefore, the higher the correlation, the more precisely heterozygosity reflects inbreeding in the population (Pemberton 2004).

In a second step, we investigated the influence of locus-specific heterozygosity (considered as a binary variable with 1 when a given locus was heterozygous, and 0 if homozygous) upon each of the social behaviours that were pointed out by the analyses (see below).

Statistical analyses

Poisson regressions were used to model the relationship between each of the behavioral response variables (aggression and affiliation) and several predictor variables defined below, so that seven distinct analyses were performed. While the behaviors of different individuals were assumed to be independent, the behaviors of each individual female were most likely correlated across her relationships, so we incorporated the identity of a given focal female as a repeated variable. The total duration of the focal sampling for each female was also included as an offset in the regressions. Because some behaviors were rarely observed during observations, resulting in excess zeros and overdispersion, we used zero-inflated Poisson (ZIP) regressions with random effects (Hall 2000) to improve statistical inference (see Supplementary Information). Following Martin et al. (2005), we conveniently used Markov Chain Monte Carlo (MCMC) sampling (Gilks et al. 1996) in a Bayesian framework (see Supplementary Information).

In addition to heterozygosity, we now describe the other predictor variables that were used in the analyses of social behaviors. Previous studies have shown that the difference in age between females affects social behaviors (Widdig et al. 2001; Smith et al. 2003; Silk et al. 2006), we therefore considered whether the social partner was a focal's peer (born in the same birth cohort) or non-peer (born in a different birth cohort), as defined by Widdig et al. (2002). Because the 51 focal females varied greatly in age, we also considered the age of the focal females. Finally, we took into account their social rank as a co-variable: we collected focal and all occurrence data on aggression in order to construct a dominance hierarchy of the adult females. We classified females as high-, mid-, and low-ranking females. Females that had not yet entered the adult dominance

hierarchy (i.e., they were less than 2 years old) were ranked directly below their mother, the rank that they would most likely assume as adults. However, we also re-did the analysis excluding the 13 females aged less than 2 years old. Results did not change. Predictor variables were examined for colinearity, using Spearman rank correlations. The effects of the three co-variables (peers/non-peers; age and social rank) on social behavior are widely discussed elsewhere (Widdig et al. 2002) and the only aim of considering them in these analyses was to use them as a control to avoid confounding effects. The results obtained on these co-variables are therefore neither presented, nor discussed here.

To test the influence of heterozygosity on social behavior, we calculated the posterior distribution that this effect was positive (or negative, respectively) as the fraction of the number of MCMC iterations in which the corresponding regression parameter was positive (or negative, respectively). As a threshold, we have considered that Bayesian significance was achieved for posterior probabilities ≥90% (Draper 2000; Link and Barker 2005), which corresponds to fairly good betting odds—about 10 to 1—in favor of an influence of heterozygosity. In contrast with the frequentist approach using P-values, the Bayesian approach allows us to identify effects of biological importance as well as statistical significance by explicitly calculating the strength of evidence of such effects while coping with effect size, that is, the magnitude and precision of the effect (Anderson et al. 2001).

In a second step, we investigated the influence of locus-specific heterozygosity (considered as a binary variable with 1 when a given locus was heterozygous, and 0 if homozygous) upon each of the two social behaviours that were pointed out by the previous analyses (i.e., aggression and grooming received). For each of them, we considered the same model structure as above, except that the covariate heterozygosity was replaced by the 13 binary variables corresponding to the 13 loci. Rather than performing separate simple linear regressions (that might have led to flaw inference), we considered the 13 explanatory variables in a multiple regression framework to account for possible co-variations between them. Those loci having a significant effect were determined using an extension of the MCMC algorithm used above—the so-called Reversible Jump MCMC (Green 1995)—that allowed us to perform model selection in a high-dimensional set of possible candidates (see Supplementary information).

Results

Heterozygosity and social behaviors

We found that focal individuals with lower mean heterozygosity received higher rates of aggression from non-kin than more heterozygous females (Table 3 and Fig. 1a), after controlling for female age and dominance rank and for the age difference between females, as well as for individual effects and other potential sources of statistical bias (see experimental procedures). However, we found no effect of heterozygosity on initiated aggression (Table 3 and Fig. 1a). We also found that heterozygosity in focal females was positively correlated with the rate at which they received grooming from non-kin, such that more

Table 3 Effect of mean individual heterozygosity on social behaviors of females ($N = 51$)

Social behaviors	Posterior median values of the regression parameter	SD	Bayesian significance	Direction
Aggressive behaviors				
Aggression initiated	0.037	0.234	0.564	No effect
Aggression received	−0.183	0.117	0.937	More homozygous females received aggression at higher rates
Affiliative behaviors				
Initiated grooming	−0.126	0.135	0.836	No effect
Received grooming	0.455	0.180	0.999	More homozygous females received grooming at lower rates
Initiated approach	0.035	0.057	0.716	No effect
Received approach	0.052	0.053	0.841	No effect
Proximity	0.010	0.065	0.559	No effect

Data were modeled using Poisson regressions accounting for repeated measurements, overdispersion and excess zeros. Note that other variables were used to control for confounding effects. The posterior median is reported for the regression parameter estimate corresponding to heterozygosity with its associated standard deviation (SD). Bayesian significance was achieved for posterior probabilities ≥90%, where posterior probabilities are calculated as the fraction of the number of times that the heterozygosity regression parameter is positive or negative, whichever is appropriate
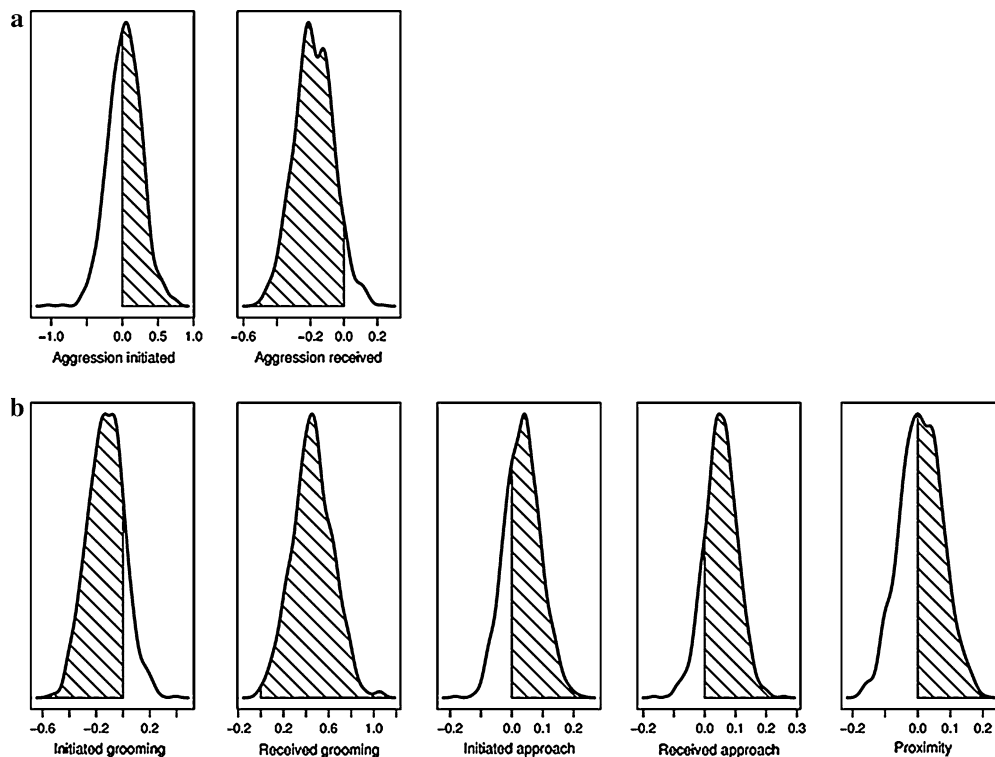
Fig. 1 Posterior probability density functions (PDF) of the influence of mean individual heterozygosity upon each social behavior. The X axes represent the range of possible regression coefficients for the effect of heterozygosity on each behavior, generated by The Markov Chain Monte Carlo (MCMC) process and smoothed with kernel density estimates. Shaded areas correspond to the posterior probabilities that the heterozygosity regression parameters are positive or negative, whichever is appropriate—referred to as Bayesian significance in Table 3

homozygous individuals received this type of affiliation at lower rates (Table 3 and Fig. 1b). This difference was not due to a decreased spatial association with conspecifics. Indeed, more homozygous females spent as much time in proximity to non-kin as more heterozygous females, and they initiated affiliative behaviors at similar rates (Table 3 and Fig. 1b). However, homozygous females were discriminated against by unrelated conspecifics; specifically, female macaques directed grooming behaviors towards more homozygous females at lower rates than they did towards more heterozygous females.

Genomewide or local effect?

Mean heterozygosity calculated for the two randomly chosen groups of loci in our analysis were not significantly correlated (mean ± sem: $r_s = -0.023 \pm 0.003$; $P = 0.408 \pm 0.029$), indicating that more homozygous individuals were not necessarily uniformly homozygous across all loci. This suggested that the effects of heterozygosity that we detected on social behavior were probably due to local effects at one or few loci rather than a genomewide effect of inbreeding.

Table 4 Associations between heterozygosity (Y/N) and social behaviors, in 51 females, at the 13 loci

Locus	Received aggression Estimate (SD)	Received grooming Estimate (SD)
D2S367	−2.90e−7 (2.39e−4)	0.010 (0.083)
D8S601	−5.15e−7 (1.49e−4)	0.027 (0.216)
D20S206	−0.138 (0.154)*	−0.045 (0.206)
D6S493	−3.03e−6 (1.59e−4)	0.023 (0.149)
D6S474	−4.09e−6 (2.66e−4)	1.069 (0.646)*
D20S476	−1.14e−6 (1.10e−4)	−0.017 (0.108)
D12S66	−6.19e−5 (0.001)	0.006 (0.083)
D12S67	−4.69e−4 (0.006)	−0.366 (0.801)
D14S255	8.35e−6 (6.56e−4)	−0.005 (0.099)
D5S820	9.63e−8 (1.61e−4)	0.007 (0.071)
D5S1470	−9.71e−8 (1.76e−4)	0.017 (0.121)
D6S266	−3.25e−5 (8.06e−4)	0.121 (0.334)
D8S271	2.27e−6 (2.72e−4)	−0.006 (0.065)

Posterior means of the regression parameters are provided along with their associated standard deviations (SD). Note that these are mode-laveraged estimates and so the associated SDs incorporate both parameter and model uncertainty

* The best model contains this single co-variate

To investigate which microsatellite loci particularly influenced the relationship between heterozygosity and behaviors, we re-analyzed our behavioral data using the 13 heterozygosities as co-variates. We found that heterozygosity at two out of 13 loci was particularly associated with variance in social behaviors (Table 4): locus D20S206 negatively influenced received aggression and locus D6S474 positively influenced received grooming. Hence, the local-effect hypothesis gained more support as a cause for association between neutral markers and fitness traits in our data than the genome-wide effect hypothesis.

Discussion

In this study, we found that genetic characteristics contribute to the social environment of an individual in complex social species such as primates, and particularly that some females—those that tend to be more homozygous at particular loci—appear to be less attractive social partners: they received less affiliation, in the form of grooming, and more aggressive behaviors from unrelated group members. The coarse-grained nature of the genetic analysis was complemented by the fine-grained nature of the behavioral data, and this combination produced an important result; the genetic characteristics of an individual influenced the manner in which its conspecifics behaved towards it. In matrilineal societies, such as most Old World primates, social relationships may confer fitness benefits e.g., through their impact on infant survival (Silk et al. 2003), through their impact on success in agonistic interactions (Sterck et al. 1997), and through the benefits of parasite removal through mutual grooming (Saunders and Hausfater 1985; see also Shutt et al. 2007). Social isolation, in contrast, may increase the risk of disease or disability through an increase of stress (House et al. 1988). This behavioral discrimination by conspecifics may indicate social selection against both less socially and less physically capable individuals. While correlations between heterozygosity and fitness parameters—i.e., reproduction and survival—are common in the literature (Crnokrak and Roff 1999; Keller and Waller 2002), less is known about the influence of genetic characteristics on social behaviors. In this study we have shown that heterozygosity at particular microsatellite loci may contribute to the quality of social bonds between unrelated individuals and that homozygous individuals could constitute less attractive social partners for their unrelated conspecifics.

Genome-wide inbreeding vs. local effects

Correlations between heterozygosity and various fitness estimates, including some measurements of social behaviors, are usually interpreted to reflect either deleterious consequences of genome-wide inbreeding (because more inbred individuals are also more homozygous), or to reflect the fact that being heterozygous at particular loci, in and of itself, confers advantages (see for example: Lieutenant-Gosselin and Bernatchez 2006).

There is a great deal of debate over whether the numerous examples of heterozygosity-fitness correlations found in several plant and animal species result from a genome-wide inbreeding or are due to one or more markers being linked to functional loci. Indeed, heterozygosity, even when measured over many markers, appears to be only weakly correlated with inbreeding coefficients (Balloux et al. 2004; Pemberton 2004; Slate et al. 2004), with the exception of populations showing high variance in individual's inbreeding (Slate et al. 2004).

Our analysis employed coarse-grained genetic characteristics and was therefore relatively uninformative about the genetic mechanisms underlying the relationship. Our results however strongly suggest that the effects found were not attributable to genome-wide inbreeding, but instead point to chromosomal regions of interest for potential candidate gene studies (Bean et al. 2004; Hansson et al. 2004). In this study, it seems likely that two of the microsatellite loci (D6S474 and D20S206) lie close enough to a balanced polymorphism for linkage to generate an association between heterozygosity and variation in behavior. Interestingly, these two loci were previously shown to be associated with certain phenotypes in humans. Locus D6S474 was recurrently shown to be associated with alcohol dependence (Camp and Bansal 1999; Sun et al. 1999), while locus D20S206 flanks a region that seems involved in human myeloid disorders (Wang et al. 1998).

Our study highlights the importance of potential local genetic effects in heterozygosity/fitness relationships, as already suggested by a growing number of studies (Bean et al. 2004; Hansson et al. 2004; Markert et al. 2004; Spielman et al. 2004; Lieutenant-Gosselin and Bernatchez 2006; Tiira et al. 2006). Two questions remain open though: why homozygosity *per se* at any given locus would confer disadvantages, and above all why these disadvantages would take the form of conspecific discrimination. Answering these questions will require the refinement of our knowledge of the genetic basis of the observed behaviors. In this respect, the recent completion of a draft sequence of the rhesus macaque genome (Rhesus Macaque Genome Sequencing and Analysis Consortium 2007) as well as the very recent identification of about 23, 000 SNPs (Single Nucleotide Polymorphisms) distributed all over the genome (Malhi et al. 2007) may help doing so.

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