American Journal of Primatology 78:44–62 (2016)

REVIEW ARTICLE

Genetic Studies on the Cayo Santiago Rhesus Macaques: A Review of 40 Years Of Research

ANJA WIDDIG[1,2,3]*, MATTHEW J. KESSLER[3,4], FRED B. BERCOVITCH[5], JOHN D. BERARD[6], CHRISTINE DUGGLEBY[7], PETER NÜRNBERG[8], RICHARD G. RAWLINS[3], ULRIKE SAUERMANN[9], QIAN WANG[10], MICHAEL KRAWCZAK[11], AND JÖRG SCHMIDTKE[12]

[1]*Research Group of Behavioural Ecology, Institute of Biology, University of Leipzig, Leipzig, Germany*
[2]*Junior Research Group of Primate Kin Selection, Department of Primatology, Max-Planck Institute for Evolutionary Anthropology, Leipzig, Germany*
[3]*Caribbean Primate Research Center, University of Puerto Rico, Punta Santiago, Puerto Rico*
[4]*Division of Laboratory Animal Resources, Robert C. Byrd Health Sciences Center, West Virginia University, Morgantown, West Virginia*
[5]*Primate Research Institute & Wildlife Research Center, Kyoto University, Inuyama, Aichi, Japan*
[6]*Department of Veterans Affairs, Greater Los Angeles Health Care System, North Hills, California*
[7]*Department of Anthropology, State University of New York at Buffalo, Buffalo, New York*
[8]*Cologne Center for Genomics, University of Cologne, Köln, Germany*
[9]*Unit of Infection Models, German Primate Center, Göttingen, Germany*
[10]*Department of Biomedical Sciences, Texas A&M University Baylor College of Dentistry, Texas*
[11]*Institute of Medical Informatics and Statistics, Christian-Albrechts University of Kiel, Kiel, Germany*
[12]*Institute of Human Genetics, Hannover Medical School, Hannover, Germany*

Genetic studies not only contribute substantially to our current understanding of the natural variation in behavior and health in many species, they also provide the basis of numerous *in vivo* models of human traits. Despite the many challenges posed by the high level of biological and social complexity, a long lifespan and difficult access in the field, genetic studies of primates are particularly rewarding because of the close evolutionary relatedness of these species to humans. The free-ranging rhesus macaque (*Macaca mulatta*) population on Cayo Santiago (CS), Puerto Rico, provides a unique resource in this respect because several of the abovementioned caveats are of either minor importance there, or lacking altogether, thereby allowing long-term genetic research in a primate population under constant surveillance since 1956. This review summarizes more than 40 years of genetic research carried out on CS, from early blood group typing and the genetic characterization of skeletal material via population-wide paternity testing with DNA fingerprints and short tandem repeats (STRs) to the analysis of the highly polymorphic *DQB1* locus within the major histocompatibility complex (MHC). The results of the paternity studies also facilitated subsequent studies of male dominance and other factors influencing male reproductive success, of male reproductive skew, paternal kin bias, and mechanisms of paternal kin recognition. More recently, the CS macaques have been the subjects of functional genetic and gene expression analyses and have played an important role in behavioral and quantitative genetic studies. In addition, the CS

Contract grant sponsor: National Science Foundation (NSF); contract grant numbers: IBN 9209510, SOC 7305516-01, SOC 39927-X00, SBR-84-06541, HOMINID grant, BCS0725183; contract grant sponsor: German Research Foundation (DFG); contract grant numbers: Nu 50/3-2, 6-1, Kr 1093/3-1, 5-2, Sa 661/1-1, Schm 373/17-1, WI 1808/1-1, 1-2, 2-1, 3-1, 5-1; contract grant sponsor: National Institutes of Health, National Center for Research Resources; contracts grant numbers: NIH-71-2003, RR-7-2115, P40-RR-01293, P40-RR-03640; contract grant sponsor: Office of Research Infrastructure Programs; contract grant number: P40-OD-012217; contract grant sponsor: The University of Puerto Rico.

Conflicts of interest: None

This work is dedicated to the memory of Andrea Trefilov (1971–2013), Corri Waitt (1975–2014), and William W. Dawson (1933–2010). We owe thanks and respect to Andrea and Bill for their important contributions to the genetic research on the Cayo Santiago rhesus macaques, and we express our gratitude and appreciation for Corri and her experimental work on color, which paved the path for recent work demonstrating that coloration, a measurable phenotype, is heritable and maintained through intersexual selection.

*Correspondence to: Anja Widdig, Research Group of Behavioural Ecology, Institute of Biology, University of Leipzig, Talstraße 33, 04103 Leipzig, Germany. E-mail: anja.widdig@eva.mpg.de

Received 17 September 2014; revised 17 April 2015; revision accepted 19 April 2015

DOI: 10.1002/ajp.22424
Published online 1 June 2015 in Wiley Online Library (wileyonlinelibrary.com).

colony has been used as a natural model for human adult-onset macular degeneration, glaucoma, and circadian rhythm disorder. Our review finishes off with a discussion of potential future directions of research on CS, including the transition from STRs to single nucleotide polymorphism (SNP) typing and whole genome sequencing. Am. J. Primatol. 78:44–62, 2016.

Key words: *Macaca mulatta*; Cayo Santiago; short tandem repeat; genetic database; paternity

INTRODUCTION

Rhesus macaques (*Macaca mulatta*) live in social groups consisting of multiple males and females. Females are philopatric and form stable matrilineal hierarchies [Gouzoules & Gouzoules, 1987], whereas males disperse from their natal group around puberty and change groups several times during their lives [Greenwood, 1980; Lindburg, 1969; Sade, 1972]. Rhesus macaques breed on a seasonal basis [Drickamer, 1974] so females' offspring can be assigned unambiguously to non-overlapping birth cohorts. Nevertheless, cohort members may still differ in age by up to 6 months. Both males and females mate with several different partners during the breeding season [Hoffman et al., 2008].

Despite much important pioneering work in both wild [e.g., Melnick & Kidd, 1983; Melnick et al., 1984a,b, 1986] and captive rhesus populations [e.g., Smith, 1981; Smith & Small, 1987; Stern & Smith, 1984], a large proportion of our current knowledge about the behavior and the genetics of free-ranging rhesus macaques originates from studies of the rhesus colony residing on the island of Cayo Santiago (CS). In the present review, we summarize over 40 years of genetic research conducted on CS animals and, partly, on CS-derived animals, i.e., monkeys born on CS but moved to the Sabana Seca Field Station (SSFS) on mainland Puerto Rico later in life. Given the large number of genetic studies conducted on CS, our primary aim is to review this particular portfolio, not genetic studies of rhesus macaques in general.

Genetic research on CS started with early blood group typing and the genetic characterization of skeletal material, continued with population-wide paternity testing using DNA fingerprints and short tandem repeats (STRs), and led to the genetic analysis of the highly polymorphic *DQB1* locus in the major histocompatibility complex (MHC). The results of the paternity studies facilitated several studies of male reproductive behavior and paternal kin recognition. More recently, the CS macaques also have been used in functional genetics studies and served as natural models for human disorders. With our review, we hope to promote continuation of the genetic research on CS, not least through prompting some potential future directions toward the end of our discourse, including the transition from STRs to single nucleotide polymorphisms (SNPs) and whole genome sequencing.

A Brief History of the Cayo Santiago Population

Cayo Santiago (CS) is a 15.2 ha island located 1 km off the southeast coast of Puerto Rico (18°09′N, 65°44′W). Since 1938, it has been home to a free-ranging colony of rhesus macaques managed by the Caribbean Primate Research Center (CPRC). All monkeys descended from 409 founders, including 40 adult males and 183 adult females, captured in 12 districts in the Lucknow area (comprising 2,500 km^2) of northern India [details in Altmann, 1962; Carpenter, 1972; Carpenter & Krakower, 1941; Rawlins & Kessler, 1986a; Kessler & Rawlins, 2016 this issue]. Since no animals have been added to the colony except through births, genetic variability on CS would be expected to have decreased over time. On the other hand, genetic drift is known to act comparatively slowly even in small populations, and none of the many investigations carried out at different times and with different methods provided any evidence of reduced heterozygosity on CS [Duggleby, 1980; Kanthaswamy et al., 2010; Widdig et al., in revision, details below].

The monkeys on CS are maintained under semi-natural conditions for behavioral and noninvasive biomedical research. Animals are provisioned with a commercial monkey diet (0.23 kg/monkey/day) but spend at least 50% of their feeding time foraging extensively on natural vegetation [Marriott et al., 1989]. Sanitized rainwater is available ad libitum from automatic water dispensers located all around the island. All animals are identified by ear notches and a unique alphanumeric tattoo [Rawlins & Kessler, 1986a,b]. Although a considerable proportion of infants do not survive their first year of life [14.1%, Widdig et al., unpublished data] and the population frequently endures natural disaster (hurricanes and disease outbreaks), removal of animals has been necessary to control the population size [see Hernández-Pacheco et al., 2013 for details on the culling strategies].

A daily census was initiated on CS in 1956 [Altmann, 1962] so that births, deaths, changes in social group membership, and losses of monkeys are generally noted within 2 days of occurrence. Between 1956 and 2014, the number of naturally formed social groups varied between 1 and 19 (mean $\pm$ SD = 7.1 $\pm$ 3.2). From the beginning, a demographic database has been maintained and updated by monthly reports comprising animal identifier, date of birth,

sex, group fissions, group memberships, maternity, maternal genealogy, parity (if applicable), date of death, or removal and cause of death (if known).

Since 1992, all members of the population have been sampled for genetic testing when trapped as yearlings for individual tattooing. To date, 4,424 animals have been genotyped for various genetic markers [see Widdig et al., in revision and below], which represents the most comprehensive genetic database of any free-ranging primate population worldwide. Veterinary intervention is minimal except during the annual trapping period when yearlings are captured, marked for identification, samples are collected (including blood for genetic analysis), and tetanus toxoid is administered [Kessler et al., 2015]. Severely injured animals are either removed from the island for treatment or euthanized in accordance with guidelines of the American Veterinary Medical Association. All animal research on CS has been approved by the CPRC and the Institutional Animal Care and Use Committee; it has also followed all legal requirements as well as principles of the American Society of Primatologists for the ethical treatment of nonhuman primates.

Early Genetics Research: Blood Group Testing

Blood group testing on CS started in November 1972 when the entire population of 293 monkeys was captured and had blood samples taken. At the time, only four social groups (F, I, J, and L) remained on the island after the 1968–1972 cull that reduced the population size from a peak of about 800 in 1968 [Duggleby et al., 1986]. Blood samples were typed for up to 11 blood group markers using rhesus isoimmune reagents [Duggleby et al., 1971; Duggleby & Stone, 1971; Sullivan et al., 1977a,b, 1978]. A total of 11 consecutive birth cohorts (1972–1983) were typed with the same methods [Duggleby et al., 1986].

Estimates of the effective population size (N_e) of the CS colony in 1972 suggested that $N_e = 70$ for the 1956 population [Duggleby, 1978a]. With such a small number of animals contributing to the gene pool, a rather low level of genetic variation was expected on CS. However, Nei's gene diversity (i.e. "expected heterozygosity") calculated for the eight blood group loci tested in November 1972 was 0.324 [Duggleby, 1980], thus exceeding by far the corresponding value of 0.130 obtained for 57 human blood group loci [Nei, 1975]. Moreover, only one of the known rhesus blood group alleles was absent from the CS macaques. Such a large variation in blood groups on CS contrasted with the low level of polymorphism at other protein loci [Buettner-Janusch & Sockol, 1977], a paucity in line with the belief that founder effects, bottlenecks, and genetic drift had greatly reduced genetic variability on CS. However, this apparent discrepancy is not surprising because (i) humans and rhesus have very different population histories and (ii) the eight rhesus loci in question had been chosen for high variability in rhesus in the first place. In fact, the blood group allele missing from CS was also rare in the rhesus population at the Wisconsin Regional (now National) Primate Research Center used to prepare the isoimmune reagents applied [Sullivan et al., 1977b].

Despite extensive male migration among social groups, six of the eight blood group loci under study exhibited significant intergroup differences in November 1972. Moreover, in the 1973 birth cohort, Nei's standard genetic distance ($D = -\log_e I$) [Nei, 1975] between groups, as calculated for seven of the loci, was 0.108 on average, indicating strong genetic subdivision of the colony [Duggleby et al., 1986]. Nevertheless, it should be noted that other studies undertaken in the 1970s using other parameters yielded somewhat different results [Buettner-Janusch et al., 1974a,b; Buettner-Janusch & Sockol, 1977; Olivier et al., 1981].

Matrilines were found to be even more differentiated for the eight blood group loci than social groups [McMillan, 1979; McMillan & Duggleby, 1981]. In November 1972, Nei's [1975] standard genetic distance was 0.082 on average among matrilines compared to 0.019 between the four social groups. Matrilines within the same group differed as much as matrilines from different groups, even when adjusted for size [McMillan & Duggleby, 1981]. Greater genetic differences between matrilines than social groups were also observed at three protein-coding genes [Olivier et al., 1981].

Inbreeding on CS was also evaluated using blood group data but no excess of homozygosity was found, neither in the population as a whole, nor within social groups [Duggleby, 1978b] or within group-specific birth cohorts [Haseley, 1980, 1984a]. By contrast, analysis of the G and H blood group systems indicated clear outbreeding, i.e., breeding among, not only within, social groups [Duggleby, 1977].

While the overall genetic subdivision, as measured by F-statistics [Duggleby, 1977], χ^2 tests for homogeneity [Duggleby, 1978b], Nei's genetic distance [Duggleby, 1978c], and gene diversity [Duggleby, 1980] remained high, variation declined subsequent to the 1972 cull [Duggleby, 1978c; Haseley, 1980; McMillan & Duggleby, 1981]. This was probably due to the rapid population increase until the next cull in 1984 [Duggleby et al., 1986]. These findings suggested that the group differences seen in 1972 were partly due to the culling process preceding the start of the genetic analyses. Even though the 1972 population had descended from a comparatively small number of females, a sizeable proportion of the adult males originated from matrilines that had been removed from the island. Thus, many potential sires at the time were unrelated, and perhaps genetically distant, to their mating partners

which might have led to an excess of heterozygotes in early studies [Duggleby, 1977; Haseley, 1980, 1984a, b]. Moreover, migration of males belonging to these removed matrilines into one of the four groups still residing on CS probably contributed different alleles to the groups, which may have added to the high level of genetic subdivision seen immediately after the 1972 cull. Since both the absolute and relative number of these migrant males declined over time, group differences declined as well [Duggleby, 1978c].

Blood group studies revealed pronounced genetic variation in the CS population, with no evidence of inbreeding [Duggleby, 1978b]. They also provided genetic evidence of social structuring within the population and of differences in fertility and mortality between genotypes, despite the small effective population size [Haseley, 1984a,b]. The results of the initial genetic studies in combination with detailed demographic data and advanced genetic methods (described below) greatly facilitated empirical testing of many behavioral hypotheses on CS and also advanced biomedical research on CS-derived macaques and their skeletal remains.

Genetic Research Based on Rhesus Skeletal Collections

The systematic collection of complete skeletal remains of CS animals was initiated in 1971 and generated an unparalleled resource for osteology, pathology, and genetics research. Some 2,394 specimen were available in November 2013 together with complete demographic records, including age at death, sex, identifier, maternity (observed or genetically confirmed), matrilineal affiliation, and social group. Systematic use of this information in a plethora of scientific studies has revealed the importance of familial relationship and, hence, genetic factors for normal growth and development, as well as for the osteopathology of the rhesus skeletal system [Dunbar, 2012; Pritzker & Kessler, 2012; Rawlins & Kessler, 1986a]. The CS skeleton collection, continuously expanded until today, not only provided an important scientific resource in the past, but also still holds great potential for future systematic research on rhesus bone and skeletal biology [see Wang et al., 2016, this issue].

The Cayo Santiago Genetic Database

Biological identification and kinship testing was revolutionized by the invention of "DNA fingerprinting" in the early 1980s [Epplen et al., 1991; Jeffreys et al., 1985; Krawczak & Schmidtke, 1998]. Arnemann et al. [1989] were the first to apply DNA fingerprinting to CS-derived rhesus macaques, namely group O transferred in toto to the German Primate Center Göttingen in 1984. Subsequently, DNA fingerprinting was used successfully in group S residing on CS, where the sires of 11 of the 15 infants (73.3%) constituting the 1989 birth cohort could be identified among 19 potential sires [Krawczak et al., 1993]. However, DNA fingerprinting failed as a means of paternity assessment in group M, which was transferred from CS to the SSFS in 1984 and had been genetically isolated ever since [Krawczak et al., 1993]. At the time, it could not be resolved whether this failure was due to increased homozygosity in group M, a different specificity of the DNA fingerprinting technique in the two groups, or simply reflected sampling error [Krawczak et al., 1993].

With the advent of polymerase chain reaction (PCR) in the late 1980s [Saiki et al., 1988], complete reconstruction of all pair-wise blood relationships became a realistic option for the CS population. While DNA fingerprinting involved targeting a single DNA sequence motif that is common to many loci in the genome, PCR paved the way for highly efficient single-locus typing. PCR primers could be designed that were specific to single copy DNA surrounding short tandem repeat (STR or "microsatellite") loci and the respective allele lengths were identified by gel electrophoresis of the amplification products [Krawczak & Schmidtke, 1998]. In this way, individual genotypes could be determined without ambiguity at enough highly polymorphic loci to allow comprehensive paternity assessment.

The systematic use of PCR for examining microsatellite variation in rhesus macaques started when 24 polymorphic human STRs were investigated in six unrelated monkeys [Kayser et al., 1996]. Twelve of the human-derived primers revealed allelic variation in rhesus DNA as well. In addition to STR analysis, genotyping of the highly polymorphic *DQB1* locus in the rhesus major histocompatibility complex (MHC) was developed as another means of kinship testing. To this end, exon 2 of *Mamu-DQB1* was amplified by PCR, digested with different restriction endonucleases, and subjected to length measurement by gel electrophoresis [Sauermann et al., 1996]. Using a combination of DNA fingerprinting, single STR analysis and *DQB1* typing, paternity and maternity was determined for several consecutive birth cohorts of groups R, S, and M from CS and CS-derived populations, respectively [Nürnberg et al., 1998]. With time, the number of human-derived primers examined in rhesus macaques doubled, and of the 51 human STRs screened for cross-species PCR amplification, 11 were found to be both present and sufficiently polymorphic (expected heterozygosity ≥ 0.6) for parentage assessment in rhesus monkeys. These markers were used for paternity testing in 100 mother–infant pairs, considering over 200 potential sires [Nürnberg et al., 1998]. Interestingly, despite a combined exclusion probability of more than 99.9%, several cases could not be solved unequivocally by STR and *DQB1* typing alone but required DNA

fingerprinting with one or more of the oligonucleotide probes (GATA) 4, (CA) 8, and (CAC) 5.

Today, genetic research in the CS and CS-derived populations is almost exclusively based upon STRs. While the early studies aimed at optimizing just 15 markers for the CS animals [Nürnberg et al., 1998; Widdig et al., 2001, 2002, 2006a,b], later studies successfully increased this number and, thus, the power of genetic analysis [Albers & Widdig, 2013; Dubuc et al., 2011; Kulik et al., 2012; Langos et al., 2013]. Eventually, a total of 42 STRs were optimized for current use [Widdig et al., in revision], and the experimental protocols have been improved over time so as to facilitate multiple-tubes [Morin et al., 2001] and multiplex typing [Bonhomme et al., 2005; Henegariu et al., 1997]. As a result of systematically sampling DNA since 1992, the CS genetic database to date comprises 4,424 animals, genotyped for an average of 27.6 ± 1.6 STRs [details in Widdig et al., unpublished data]. Paternity has been determined for 4,004 individuals (90.5%) and maternity, as derived from behavioral observations, could be confirmed genetically for 3,966 of 4,034 mother-offspring pairs (98.3%). Based upon these data, pedigrees covering several generations can be reconstructed [Widdig et al., in revision].

Since estimates of inbreeding (e.g. from multilocus heterozygosity) are known to correlate only weakly with true (pedigree-based) inbreeding coefficients [e.g., Overall et al., 2005], it was worthwhile reinvestigating the level of inbreeding in the CS population on the basis of the pedigree data that have become available over time. Simulations suggested that three generations of pedigree data contain $\geq$80% of the information on inbreeding in the bottom generation [Balloux et al., 2004]. Therefore, inbreeding coefficients were calculated for CS monkeys with completely known ancestry going back three (2,115 animals from 23 consecutive birth cohorts) or four generations (333 animals from 11 consecutive cohorts). These data revealed that inbreeding was rare and had not increased over time [Widdig et al., in revision], thereby supporting earlier reports on more distant generations (i.e., the 11 birth cohorts from 1972 to 1983) that were based upon less informative blood group markers [see above and Duggleby et al., 1986].

Paternity-Based Studies Conducted on Cayo Santiago

With the establishment of the CS genetic database, it became possible to combine the available paternity information with demographic, morphological, and behavioral data. This unique setting facilitated research on the relevance of male attributes (e.g., dominance rank) for male reproductive success, on the unequal share in male reproductive output (reproductive skew), on the importance of paternal kin bias for the evolution of social behavior, and on mechanisms of paternal kin recognition.

Male dominance and reproductive success

One important focus of primate research is the relationship between male dominance rank and reproductive success because reproductive competition is one of the driving forces of evolution through sexual selection [Darwin, 1871; West-Eberhard, 1979]. Higher dominance rank provides preferential access to sexually receptive females and often coincides with greater sexual activity [reviewed in Berard et al., 1993]. Furthermore, high male dominance rank has been assumed to result in higher levels of reproductive success [cf. Cowlishaw & Dunbar, 1991]. Nowadays, there is ample evidence for a positive association between male dominance and reproductive success in various primate species, both captive and wild populations [e.g., Altmann et al., 1996; De Ruiter et al., 1994; Paul et al., 1993; Smith, 1981], although this relationship may be either weak or lacking in others [e.g., Inoue et al., 1991] or varying over time even in the same population [reviewed e.g., in Alberts, 2012; Di Fiore, 2003; Ellis, 1995].

Berard et al. [1993, 1994] were the first to use the new DNA typing technologies for behavioral studies in the CS population, more specifically in the 1989 birth cohort of group S [Krawczak et al., 1993; see above]. Paternity could be determined for 11 of the 15 infants, including seven infants that were sired by group males and four infants sired by males from other groups on the island. In this study, no significant correlation was found between male dominance rank and reproductive success; some 40% of the high-ranking and 60% of the low-ranking males sired at least one offspring even though the former had significantly more consorts than the latter [Berard et al., 1993].

The early findings notwithstanding, later studies on CS using larger samples of 31 and 28 infants with assigned paternity, respectively, found that high-ranking males in fact sired more offspring than low-ranking males [Dubuc et al., 2011; Widdig et al., 2004], although the alpha male was never the most successful sire [Dubuc et al., 2011; Widdig et al., 2002]. When testing the priority-of-access model that predicts male reproductive output to be a function of female synchrony and male dominance [Altmann, 1962], a study combining 2 years of mating and paternity data revealed that the model did not predict male reproductive success with much precision. In fact, the model overestimated the reproductive success of high-ranking (particular alpha) males and underestimated the success of middle- and low-ranking males [Dubuc et al., 2011]. Since male rhesus macaques queue, rather than fight, for dominance [Berard, 1999], the alpha male is not

necessarily the strongest or most attractive male. Consequently, the most successful sires were high ranking (but not top-ranking) males, suggesting that attributes other than dominance rank contribute to male reproductive success [Dubuc et al., 2011]. Similar, male dominance correlated positively with male mating success overall, but the alpha male did not obtain the largest mating success [Dubuc et al., 2011].

Although female rhesus macaques lack the sexual skin swelling of other primates, their facial skin coloration increases significantly during the fertile stage suggesting that males may use this signal to assess the fertility status of females [Dubuc et al., 2009]. Since dominant males can be expected to be able to monopolize matings with fertile females, another study on CS specifically addressed the timing of mate guarding by high-ranking males, using behavioral, hormonal, and paternity data. The results suggested that mate-guarding by dominant males may only partly match the female fertile phase, in that the former explained no more than 30–40% of fertilizations (i.e., births with assigned paternity) [Dubuc et al., 2012]. This indicates that male rhesus may have only limited information on the exact timing of female ovulation, which provides an opportunity for female mate choice and avoidance of monopolization by dominant, but less attractive, males at the time of ovulation [Dubuc et al., 2012]. Indeed, previous studies on CS yielded evidence of female mate choice because female rhesus were able to resist mating with their consorts and to solicit low-ranking males more often than high-ranking ones [e.g., Bercovitch, 1997; Chapais, 1983; Manson, 1992].

Consistent with the idea that female mating strategies do not serve to maximize the reproductive success of high-ranking males, a relatively high level of extra-group paternity (24.7%) was noted in a 6-year study of 247 infants from group R [Widdig et al., 2004] ranging within the proportion of extra-group paternity reported for wild primate populations [reviewed in van Noordwijk & van Schaik, 2004]. Finally, paternity analysis of twins, which are rare in the CS populations, revealed that twins can have different fathers. In the actually observed case, one father was a natal male from the dominant matriline while the other was an extra-group male [Bercovitch et al., 2002].

Other factors influencing male reproductive success

In contrast to dominance rank, age turned out to be an important determinant of male reproductive success in rhesus macaques [Bercovitch et al., 2003]. Thus, a preliminary analysis of 21 infants born into group R revealed that prime age males between 9 and 12 years sired more offspring than expected by chance alone, while younger or older males sired fewer offspring than expected [Bercovitch, 1997]. A more detailed analysis, based upon a decade of data on 746 infants from multiple groups, confirmed and expanded these findings [Bercovitch et al., 2003]. Nearly half of the potential sires had no offspring at all, while prime age males produced significantly more progeny than expected. The youngest sire was a 3.8-year-old male, whereas the average age at first reproduction was 7.5 years, approximately the age at which full body size is achieved [Bercovitch et al., 2003].

The relationship between male body condition and reproductive output turned out to be more complicated. On the one hand, body mass index (BMI) remains relatively stable in male rhesus from 9 to over 20 years of age, so that BMI cannot explain the age dependence of male reproductive output [Bercovitch et al., 2003]. On the other hand, it could be shown that sires accumulate more fat during the pre-mating season than do non-sires [Bercovitch, 1997; Bercovitch & Nürnberg, 1996], which potentially enables them to forego feeding during the mating season despite the increased energy demand. Similarly, a comparative study of age-matched males in groups R and M revealed that body condition, together with age and dominance rank, influences male reproductive success, while canine size does not [Bercovitch & Nürnberg, 1997].

Studies of the CS macaques also provided invaluable insights into the genetic organization of the rhesus major histocompatibility complex (MHC) class II region. Moreover, the paternity information available on a large number of free-ranging macaques allowed direct investigation of the possible selective pressure resting on the MHC region. Genotyping of the polymorphic *Mamu-DQB1* locus, which is tightly linked to *DQA1* and the *DRB*-region in rhesus macaques, revealed that males heterozygous at this locus sired significantly more offspring than homozygotes, irrespective of the actual male genotype [Sauermann et al., 2001]. Such effect was not observed in a captive group with similar genetic background but under veterinary care. Furthermore, males who were heterozygous at *Mamu-DQB1* were more likely than homozygotes to reproduce at all [Widdig et al., 2004]. These results suggest that MHC heterozygosity may be a strong determinant of male reproductive success in free-ranging rhesus macaques.

Recent research suggests that social skills also impact male fitness because strong social bonds among male Assamese macaques, *M. assamensis*, were found to be linked to coalition formation, which in turn predicted future dominance and increased male reproductive success [cf. Schülke et al., 2010]. Combining behavioral and paternity data from group R on CS, it was also shown that the probability of male support in favor of females had no influence on male reproductive success per se even though high sociality in a given male–female dyad increased the

probability of paternity of the respective male [Kulik et al., 2012]. Likewise, male–male sociality was found to be the most important predictor of male–male support because males with a male friend were more likely to receive support (from that friend) when involved in conflicts. These results add further evidence of male sociality affecting male fitness in primates but also suggest that, in species in which males queue for dominance, it seems less likely that males can increase their fitness via coalitionary support [Kulik et al., 2012].

An unequal share in male reproductive output (reproductive skew)

In some primate populations, a single male produces all or most of the offspring in a given year [e.g. Altmann et al., 1996] while, in others, male reproductive output is more evenly distributed among group males [e.g. Strier et al., 2011]. The first scenario, also referred to as "male reproductive skew," seems to be more common one among primates although the actual level of reproductive skew varies between species [reviewed in Widdig, 2013]. Indeed, much empirical and theoretical research has been done in the past on the extent to which male primates share or do not share reproductive opportunities with other male group members [Kutsukake & Nunn, 2009; Ostner et al., 2008; Port & Kappeler, 2010; Widdig, 2007, 2013].

One of the first studies testing models of male reproductive skew in primates was carried out on CS. Using paternity data of 247 infants born in six consecutive birth cohorts of group R, male reproduction measured by Nonac's B index was found to be significantly skewed toward a few successful sires suggesting "limited control" over reproduction by dominant males [Widdig et al., 2004]. The top troop sire produced 20–30% of offspring over time, while the percentage of troop males that produced no offspring at all ranged from 70–80% [Widdig et al., 2004]. A similar investigation of smaller CS group V, involving 28 infants, also yielded evidence for significantly skewed male reproduction in two consecutive breeding seasons (again measured by Nonac's B index). The top troop sire produced 35.7% of offspring in the study period, while 60% of troop males sired no offspring at all [Dubuc et al., 2011]. Taken together, these two studies put male reproductive skew in rhesus macaques (at least on CS) at an intermediate level compared to other primate species [Dubuc et al., 2011].

A more recent study exploiting the comprehensive paternity data available on CS revealed that lifetime reproductive success of male rhesus macaques is also significantly skewed [Dubuc et al., 2014b]. While 37% of males that reached reproductive age produced more than the average number of offspring in their life, 17% never reproduced at all. The higher percentage of non-sires reported in short-term studies not only indicates the potential relevance of the individual life span in this context but also highlights the need for long-term studies. Indeed, the length of the reproductive lifespan has an impact on male lifetime reproductive success although less so than male fecundity (measured by the reproductive rate throughout reproductive life; coefficient of determination: 25% vs. 60%), suggesting that some direct male–male competition may take place on CS [Dubuc et al., 2014b].

Compared to the causes of male reproductive skew, its consequences are generally less well studied [for discussion see, e.g., Di Fiore, 2003, 2012; Melnick, 1987; Storz, 1999]. One possible consequence of the majority of matings and/or paternities being confined to a few males is the potential spread of sexually transmitted diseases [Kutsukake & Nunn, 2009]. Another consequence of only a few males contributing to the gene pool of the next generation would be a greater opportunity, for example, for sexual selection through traits that are associated with large reproductive success [Dubuc et al., 2014b] and for kin selection through increased levels of within-group relatedness. Since breeding tenure is often restricted in male primates because high-ranking breeders are frequently replaced by others [reviewed in Widdig, 2013], male reproductive skew would also result in age cohorts comprising many pairs of paternal half-siblings [Altmann, 1979; Di Fiore, 2003; Widdig et al., 2004] and render social groups genetically structured according to age [Altmann et al., 1996].

Investigations of paternal kin bias on Cayo Santiago

The long-term genetic and demographic data available for the CS colony allowed the degree of relatedness among pairs of individuals to be inferred directly from pedigrees, rather than through estimates of dyadic relatedness based on STR markers. The latter has been shown to be prone to error. For example, an analysis of long-term genetic and demographic data of wild baboons revealed that the mean relatedness obtained from genotype data corresponded well to their expectation from pedigrees (i.e., each distinct kin category inferred from pedigree data corresponded to the expected mean relatedness). At the level of the individual dyad, however, this correspondence was notably poorer [Csillery et al., 2006; Van Horn et al., 2008]. Although the pedigree-based approach is less suitable for primate field studies because the degree of relatedness between members of the founder population is usually unknown, the maximum error arising from ignoring relatedness between grandparents is only 0.03125 (which occurs when the kinship coefficient equals 0.5) [Van Horn et al., 2008]. Such a small difference is probably irrelevant at the individual behavior [cf. Chapais et al., 1997].

However, it has been emphasized that the systematic misclassification of pair-wise relatedness at the study level could lead to false conclusions about the impact of kinship on social behavior [Van Horn et al., 2008; Widdig, 2013]. For studies addressing whether individuals give preferential treatment to their kin over non-kin (kin bias) and whether kin can be distinguished from non-kin (kin recognition) [cf. Penn & Frommen, 2010] pedigree-based approaches, therefore, seem more appropriate.

Evidence for both kin bias and kin recognition has been found in the CS population. Earlier studies demonstrated strong affiliation bias to prevail among maternally related females [e.g., Kapsalis & Berman, 1996], as was to be expected in matrilineal societies with philopatric females [reviewed in Silk, 2002]. However, less was known about whether the behavior of rhesus macaques toward their paternal kin was also biased. As has been mentioned above, many members of the same age cohort will be paternal half-siblings because male reproduction is skewed and male breeding tenure is limited to a few years [Widdig et al., 2004]. Paternity studies of group R revealed that individuals have more paternal half-siblings (9.9 ± 9.7) than maternal half-siblings (2.6 ± 1.4) or full siblings (0.1 ± 0.4) in the same group [Widdig et al., 2004]. In the first study ever on paternal kin bias among philopatric female primates, also carried out on CS, adult females were found to have the closest affiliative bonds with their maternal half-sisters, but also to significantly affiliate more with their paternal half-sisters than with unrelated females [Widdig et al., 2001]. Moreover, this paternal kin bias was most pronounced among peers (born in the same birth cohort) than non-peers (born into different birth cohorts), suggesting that age proximity might be an important cue for paternal relatedness. Evidence of paternal kin discrimination was also found for some other behavioral contexts [group fission, agonistic support: Widdig et al., 2006a,b], but not for all [dyadic aggression: Widdig, 2002; Widdig et al., 2002].

Studies of other primate species provided additional evidence of paternal kin bias among philopatric females [rewiewed e.g., in Widdig, 2013]. However, little is known about kin bias, particularly paternal kin bias, in the dispersing sex (i.e. males, in the case of rhesus macaques). Kin availability is expected to decrease dramatically upon natal dispersal and to diminish further by subsequent migration. A first study combining demographic, behavioral, and genetic data on natal dispersal in CS rhesus macaques confirmed that the majority of natal immigrants to a given social group were indeed unrelated (80.7%), even when considering only familiar males (i.e. males who grew up in the same natal group and dispersed to the same non-natal group) [Albers & Widdig, 2013]. Among familiar natal migrants, kinship shapes patterns of spatial proximity in a way similar to females in that migrants sit closer to maternal kin, followed by paternal kin and non-kin [Albers & Widdig, 2013]. Around maturation, when females start to breed and males prepare for departure from their natal group, animals of either sex form their strongest bonds with maternal kin. However, males had a higher probability than females of the same age to associate with paternal kin rather than unrelated group members, suggesting that males search for alternative bonding partners with whom they can potentially migrate [Widdig et al., 2016, this issue].

As has been mentioned above, the extensive pedigree data available on CS revealed that both paternal and maternal inbreeding are rare in the colony [Widdig et al., in revision]. The addition of mating data would allow future studies to investigate whether mating between paternal kin is actively avoided, or whether post-copulatory mechanisms result in early fetal loss in the case of paternally related sires.

Finally, a recent study of male-infant associations on CS showed that sires are more likely to affiliate with their own offspring than non-sires are to affiliate with unrelated infants [Langos et al., 2013]. This preference is independent of the presence of the infant's mother. Males rarely show aggressive behavior toward infants [Langos et al., 2013], but they also do not provide agonistic support to their own offspring [Kulik et al., 2012], as has been reported for other species [Buchan et al., 2003]. A bias toward father–offspring affiliations might be surprising given that female rhesus macaques mate highly promiscuously [Lindburg, 1971], leading to uncertainty about paternity, and given that top-ranking males ensure paternity rather inefficiently through mate-guarding of fertile females [Dubuc et al., 2012]. Hence, further studies on the mechanisms of paternal kin recognition in rhesus macaques are well warranted.

Mechanisms of paternal kin recognition

As pointed out in the previous section, male rhesus macaques on CS exhibit an intermediate level of reproductive skew compared to other primate populations [Dubuc et al., 2011]. This means that only a certain proportion of dyads of peers (i.e., infants sired in the same breeding season) will be paternally related, whereas the remainder will be unrelated peers. Therefore, although age proximity is a likely proxy to relatedness in paternal kin recognition (see above), additional mechanisms, such as matching phenotypes, may have evolved [reviewed in Widdig, 2007]. "Phenotype matching" suggests that individuals "learn" kin templates, either from self or father, and use this knowledge later to judge their possible paternal relatedness to others. Candidate phenotypes included odor, bodily appearance, and voice. Over time, substantial empirical evidence for phenotype matching as a means of paternal kin recognition in

primates has accumulated [reviewed in Widdig, 2013] and most of the relevant studies were conducted on CS.

To assess whether the acoustic modality is used in paternal kin recognition, a recent study on CS investigated the extent to which female rhesus macaques can discriminate between calls from paternal half-sisters and unrelated females, and whether familiarity and/or phenotype matching was the underlying mechanism. Indeed, when confronted with play back calls, females responded more often to calls from paternal half-sisters than to calls from unrelated females. This discrimination ability was independent of the level of familiarity between caller and recipient because females preferentially responded to calls from paternal half-sister even when they never lived in the same social group as the caller. These experiments provided the first evidence for acoustic phenotype matching in primates after carefully controlling for familiarity [Pfefferle et al., 2014b].

Visual phenotype matching was also suggested as a mechanism of paternal kin recognition by a study conducted on CS rhesus macaques. Paternal and maternal resemblance to both sons and daughters was found to be detectable even to human observers when presented with frontal images of adult animals [Kazem & Widdig, 2013]. Drawing upon the extensive pedigree and demographic data from CS, a follow-up study employed a similar set-up in the field. Monkeys were presented with facial images of paternal half-siblings and unrelated individuals simultaneously, with both individuals being unfamiliar to the test subject. Intriguingly, test subjects systematically biased their inspection time toward non-kin when the animals pictured were of the same sex (potential threats), relative to when they were of the opposite sex (potential mates). This result provides additional evidence for the importance of visual phenotype matching, and was the first demonstration in any primate species of the spontaneous recognition of own paternal relatives, using facial cues under natural conditions [Pfefferle et al., 2014a].

Studies on Functional Genetics, Behavioral Genetics, Gene Expression, and Heritability

Serotonin transporter gene promoter variation associated with reproductive behavior

Genetic factors have long been implicated in the etiology of human psychiatric diseases, as well as in shaping normal behavior in humans. However, the observed associations between genetic polymorphisms and psychological traits were usually weak and difficult to reproduce [Kendler, 2013]. One of the major impediments of such psychogenetic studies appears to be the enormous complexity of human behavior. Primate models, in principle, could provide some insight into the genetic basis of human behavior as well, particularly since behavioral patterns are often more easily studied and more objectively ascertained in animal models than in humans.

Initially, the genes involved in neurotransmitter metabolism were screened for polymorphisms in rhesus macaques that could be used in association and linkage studies in this species [Trefilov et al., 1999]. Candidate genes selected on the basis of whether sufficient DNA sequence information was available for the human ortholog included the dopamine and serotonin receptors and transporters, and tyrosine hydroxylase. A total of 13 SNPs in five different genes were identified in rhesus macaques, including *DRD1*, *DRD3*, *DRD4*, *HTR1D*, and *HTT*, and allele frequencies were estimated from 70 to 150 typed chromosomes [Trefilov et al., 1999].

While the above investigation was in progress, another study identified a functional polymorphism in the promoter region of the human serotonin transporter gene (*SLC6A4*) that had an orthologous counterpart in rhesus macaques [Lesch et al., 1996, 1997]. In both humans and macaques, the polymorphism consists of a variable number of tandem repeats (VNTR) of the core sequence $(C)_7$AGCAT $(C)_6$TGCA. The long (L) allele has 17 repeat units in humans and 24 repeat units in rhesus. The short (S) allele lacks 44 and 22 bp in humans and rhesus, respectively, due to a deletion involving repeat units VIII and IX [Lesch et al., 1996; Trefilov et al., 2000]. In humans, this polymorphism is functional in that the S allele reduces the transcriptional activity of the serotonin transporter gene relative to the L allele. Moreover, the polymorphism was shown to be associated with anxiety and depression-related personality traits [Lesch et al., 1996; for review of confirmatory and non-confirmatory data see: Gelernter, 2014].

The age at which male rhesus monkeys leave their natal group is an important marker of male social behavior and is known to be related to serotonin metabolism [Kaplan et al., 1995; Mehlman et al., 1995]. Decreased serotonin levels have been found to be associated with a young age at natal dispersal in male rhesus macaques, whereas increased serotonin levels are associated with delayed migration from the natal group [Kaplan et al., 1995; Mehlman et al., 1995]. This link prompted a study of the relationship between the *SLC6A4* promoter VNTR mentioned above and age of male dispersal in the CS colony [Trefilov et al., 2000]. In rhesus macaques most, but not all, males migrate between 3 and 6 years of age [Berard, 1990]. The study by Trefilov et al. [2000] revealed that males that were SS homozygous for the *SLC6A4* promoter VNTR migrated substantially earlier than LL homozygotes (mean age $\pm$ SD $= 57.1 \pm 2.6$ vs. 71.5 ± 2.1 months). Interestingly, the mean age at dispersal of LS heterozygotes was found to be intermediate (63.5 ± 1.5 months). Trefilov et al. [2000], therefore, speculated that heterozygotes may have a selective

advantage over both, LL homozygotes (lower dispersal costs, longer association with the new social group) and SS homozygotes (higher reproductive success in the natal group). In this case, the observed *SLC6A4* promoter polymorphisms would have represented a classical example of balancing selection in a primate species.

In fact, the mean number of offspring sired in the study by Trefilov et al. [2000] was lower for homozygotes (LL: 2.6; SS: 2.8) than for heterozygotes (LS: 3.4), although the difference was only of borderline significance ($0.05<p<0.10$). This notwithstanding, an in-depth analysis of the reproductive life history of individual males provided evidence that the *SLC6A4* promoter VNTR was significantly associated with a different reproductive timing [Krawczak et al., 2005]. Heterozygous males exhibited an increasing rate of reproduction until the age of 11 years, followed by a constant decline thereafter, whereas both homozygous genotypes showed a pronounced reproductive mode at 7 to 8 years and a second mode around 16 to 17 years of age. At least in part, these findings were explicable by age at male natal dispersal representing a critical determinant of genotype-specific reproductive opportunities in early adulthood. While SS homozygotes, which migrated early, initiated reproduction mainly in non-natal groups, LL homozygotes dispersed late and were therefore likely to first reproduce in their natal groups. Heterozygotes, in contrast, migrated at an intermediate age, thereby delaying their reproductive onset for some time.

Reproduction in rhesus macaques is influenced by female choice, with females preferring mating partners that are novel to their own social group [Berard, 1999; Bercovitch, 1997; see above]. In view of a study by Cherkas et al. [2004], who reported genetic factors to influence the number of sexual partners and the level of infidelity in women, it appeared possible that the *SLC6A4* promoter VNTR also influenced female reproductive choice in rhesus macaques. When Trefilov et al. [2005] scrutinized the 139 CS females with at least two offspring of known paternity, some 115 (83%) were found to have conceived all their infants from different males. Interestingly, the proportion who had at least two offspring from the same male (17%) differed significantly between different female VNTR genotypes (LL: 20%; LS: 10%; SS: 38%). Thus, LS females appeared to be more promiscuous than SS females, although it remained unclear whether this difference was due to a dominant effect of the L allele or reflected heterosis.

Behavioral genetics and gene expression studies

More recently, Higham et al. [2011] investigated the genetic and neuroendocrine basis of mother–offspring affiliation in CS animals. A previous study had revealed that variation in the mu-opioid receptor (*OPRM1*) gene correlated with differences in mother–offspring affiliation in captive rhesus in that infants carrying a G allele (genotype GC or GG) responded with more distress to the separation from their mother and spent more time in contact with them after reunification than CC homozygous infants [Barr et al., 2008]. It was also known that, in lactating females, a high level of oxytocin is associated with high levels of grooming and nursing of infants. Thus, combining data on the *OPRM1* SNP and the oxytocin level of adult females with data on mother–offspring affiliation from CS, it emerged that lactating females with a G allele had higher oxytocin levels, but also prevented separation from their infants more frequently than females homozygous for the C allele [Higham et al., 2011].

Combining data on affiliation and aggression with genotypes of 13 STRs, the relationship between multi-locus heterozygosity and various complex social behaviors was studied in 51 unrelated female rhesus macaques from CS. Although this is a commonly used approach, it has been shown that genome-wide heterozygosity are best measured by a large number of markers [e.g., Miller et al., 2014]. In the CS study, based on previous findings, it was predicted that homozygotes would be less socially involved than heterozygotes. Indeed, females with a lower degree of heterozygosity received more aggression and less affiliation than females with higher degree of heterozygosity, suggesting that homozygotes may be less attractive than heterozygotes as social partners for unrelated conspecifics [Charpentier et al., 2008].

The first study of gene expression on CS was done on hair follicles in order to determine whether expression of pigmentation genes differed between rhesus macaques of different coat color. To this end, tuft samples were analyzed for reflectance (color) and the expression of seven key pigmentation genes (*MITF*, *MC1R*, *MGRN1*, *ATRN*, *SLC24A5*, *TYRP1*, and *DCT*). However, none of the genes showed any significantly different expression in light, dark and intermediate hair tufts, suggesting that coat color variation is unlikely to be due to differences in gene expression, at least for the pigmentation genes tested [Bradley et al., 2013].

Heritability studies on Cayo Santiago (quantitative genetics)

An increasing number of heritability studies have also taken advantage of the pedigree data available for the CS population. One of these studies [Brent et al., 2013] examined whether social networks are heritable. Using methods of quantitative genetics, the authors linked variation in social behavior to serotonin gene polymorphisms. Both affiliative and aggressive behavior were found to be significantly heritable and also to be related to reproductive output. Another study underscored

even more the relevance of quantitative genetic techniques for primate behavioral studies, particular in free-ranging and wild primate populations [Blomquist & Brent, 2013]. Here, a Poisson generalized linear mixed model was used to analyze the number of individuals staying in close spatial proximity to a given adult rhesus macaque. It was found that the propensity to share spatial proximity with group members was heritable. Later, the heritability of personality and its consequences for fitness were studied on CS, again using quantitative genetic models [Brent et al., 2014]. Six personality dimensions were noted in adult female rhesus macaques, with heritability ranging from 14% to 35% across dimensions. However, the personality dimensions were not associated with fitness as measured by female reproductive success [Brent et al., 2014].

In both macaques and baboons, dominant females are known to mature earlier than subordinates [Altmann et al., 1988; Bercovitch & Berard, 1993; reviewed in Ellis, 1995]. A study was, therefore, undertaken on CS to examine how female dominance rank and age of first reproduction are influenced by shared additive genetic and environmental effects. Higher-ranking females were found to mature earlier than low-ranking ones. The CS pedigree data then revealed a significant heritability (0.217) of the age of first reproduction [Blomquist, 2009a, 2012]. Since the total number of offspring of a given female is dependent upon her lifespan [Bercovitch & Berard, 1993], another study was undertaken to investigate the potential trade-off between age of first reproduction and female lifespan [Blomquist, 2009b]. Age of first reproduction and adult survival rates were significantly genetically correlated, suggesting that some of the genetic causes that lead to early reproduction also result in low adult survival. However, both traits showed only low-to-moderate heritabilities (0.128–0.386), indicating that non-genetic causes contributed considerably more to the phenotype than genetic causes. As the non-genetic causes of the two traits were not correlated, the overall phenotypic relationship between age of first reproduction and lifespan was small.

Blomquist used two analytical approaches (regression coefficients and variance components) to examine whether the offspring mortality rate was associated with any maternal attributes (summarized as maternal effects) [Blomquist, 2013]. A large number of dyads were investigated on CS, considering different periods of offspring life (birth to 900 days). Significant maternal effects (e.g., maternal age) on offspring death were revealed by both analytical approaches, particularly during early offspring life [Blomquist, 2013].

For 15 morphological measurements from skeletons (cranium and limb sizes) and six life history traits of adult females, Blomquist furthermore investigated the magnitude of genetic and residual variation of these traits. The mean heritability of the morphological traits was 0.50, compared to 0.22 for the life history traits. This result corroborated the theoretical expectation that lower heritability is characteristic of fitness-associated traits [Blomquist, 2009c].

Most recently, red skin ornaments of CS rhesus macaques, a rare mammalian trait previously shown to be involved in female mate choice [Dubuc et al., 2014a], was assessed for its heritability and for its influence on fecundity, two preconditions for the trait to be subject to selection [Dubuc et al., 2014c]. Using facial images and pedigree data of the CS macaques, dark red males were also found to be able to reach high-ranking positions. Some 25–30% of the variation in skin darkness and 7–13% in redness were shown to be heritable in both females and males, with confidence intervals not overlapping 0. Furthermore, redder (but not darker) females reproduced at higher rate [Dubuc et al., 2014c]. Together with results of behavioral [Dubuc et al., 2014a] and experimental work [Waitt et al., 2003] showing female sexual attraction to male skin darkness, this work provides evidence that the trait has been subject to intersexual selection.

Rhesus Macaques as Natural Models for Adult-Onset Macular Degeneration and Glaucoma in Humans

Rhesus macaques provide an excellent animal model for human retinal drusen [Bellhorn et al., 1981; Dawson et al., 1989a,b, 2008; Fine & Kwapien, 1978], the hallmark of age-related macular degeneration (AMD) which is the major cause of visual impairment of the elderly worldwide [Bird, 2003; Friedman et al., 2004]. Drusen are deposits on the Bruch membrane and probably derive from the retinal pigment epithelium. The pathology of drusen in humans and macaques is very similar at both the clinical and ultrastructural level [Dawson et al., 2008]. Drusen formation affects no more than 6% of the aging rhesus macaques in the US primate facilities [Bellhorn et al., 1981; Stafford et al., 1984], but the CS population is exceptional in that almost 60% of the animals living there are affected [Hope et al., 1992]. Both environmental and heritable factors have been implicated in drusen development, and human twin research [Gorin et al., 1999], as well as lineage-specific prevalence figures in rhesus macaques [Hope et al., 1992] hinted toward a genetic etiology of drusen formation in both species.

In humans, affected sib-pair analyses [Weeks et al., 2000] and genetic association studies [Schick et al., 2003; Seddon et al., 2003] identified candidate genes for drusen susceptibility on different chromosomes, thereby pointing toward locus heterogeneity for this condition. Prompted by these findings, Singh

et al. [2005] undertook the first study in a nonhuman primate to identify the genetic component of macular disease. Their study group comprised 52 animals aged 7–22 years that were randomly selected from CS-derived social group M residing at the SSFS. The authors screened the rhesus orthologs of human genes implicated in macular pathology for polymorphisms. Seven polymorphic loci were identified and subsequently tested for an association with drusen formation. The *IMPG1* locus was first identified as a promising candidate, but subsequent attempts to replicate this finding in another CS-derived group (group O) at the German Primate Center were unsuccessful. Nevertheless, although the original *IMPG1* risk haplotype was not confirmed, this did not exclude *IMPG1* or closely linked genes from contributing to drusen formation [Singh et al., 2007].

A major breakthrough toward establishing rhesus macaques as an animal model for human maculopathy was the finding by Francis et al. [2008] that the two species share common susceptibility genes for AMD, namely *ARMS2* and *HTRA1*, both of which are transcribed in the retinal pigment epithelium. In order to corroborate these results, Singh et al. [2009] genotyped the same cohorts as used in the 2005 and 2007 studies (116 animals) for *ARMS2* and *HTRA1*. Several novel variants were identified in both genes and a significant disease association was confirmed. However, the authors also observed that the disease association was entirely attributable to one of the *HTRA1* markers, thereby supporting the hypothesis that the *HTRA1* gene region plays an important role in drusen formation in different groups of rhesus macaques.

The above studies were developed further by Pahl et al. [2012] who identified additional polymorphisms in pronounced linkage disequilibrium with one another in the *ARMS2*/*HTRA1* gene region, hence a situation strongly resembling that observed in humans [Fritsche et al., 2008]. The authors argued that the risk gene would not become identifiable through statistical methods alone and stressed the need for additional functional studies. In a subsequent article [Pahl et al., 2013], the same group showed that a drusen-associated *HTRA1* promoter SNP, rs196357513, destroys a predicted binding site for vitamin D receptor. Since patients with vitamin D deficit are at increased risk for AMD, the authors analysed the relationship between rs196357513 genotype on the one hand, and rhesus gene expression of *HTRA1* on the other. They concluded that vitamin D-dependent downregulation of *HTRA1* increases the risk for drusen formation in rhesus macaques.

In addition to drusen, the CS rhesus macaques were also found to have naturally occurring normotensive and hypertensive primary open-angle glaucoma (POAG). Comparison of diurnal intraocular pressure (IOP) variation in these animals to that in normal, healthy monkeys revealed that the biggest range of IOP variation was found in the hypertensive glaucoma monkeys [Komaromy et al., 1998]. Further studies revealed that the CS animals had significantly higher intraocular pressure and larger optic disc cups than monkeys from random sources in other colonies. The distribution of the abnormalities was not uniform: the incidence of high IOP was more than 25% in one social group [Dawson et al., 1998]. Subsequently, a small group of CS-derived monkeys with high IOP was established in Florida to breed more of these animals for study and to discern the inheritance pattern of glaucoma [Dawson et al., 2005].

The Golden Macaques of Cayo Santiago

Pickering & van Wagenen [1969] first described the "golden" rhesus macaque. This rare phenotype, estimated at 1 in 10,000 births in the wild, is characterized by a light red or gold-colored coat color with light skin pigmentation. Their breeding experiments with golden and normal rhesus indicated that this trait was autosomal recessive and due to a single gene.

The golden macaques on CS range in color from gold to blonde [Kessler et al., 1986]. All have the typical rhesus two-toned torso color distribution and coat color penetration [Bradley et al., 2013; Dawson et al., 2004; Kessler et al., 1986a]. They have light skin pigmentation and most have blue eyes. At least one golden macaque might have been present in the founding population [cf. Sade et al., 1985], but none were reported to have been born until 1972 [Kessler et al., 1986; Rawlins & Kessler, 1983].

The sires of 24 of the 42 golden macaques born between 1981 and 2014 on CS have been identified through genotyping. Of these, five males sired two golden macaques each with different females. With one exception, all duplicate births of goldens from the same sire occurred in the same matriline. All were born to phenotypically normal females and males (when paternity could be established) with the exception of one golden macaque born to a golden mother and two golden sires accounting for two golden infants. Fifty percent of these births occurred in the same group, namely group I (matriline DM). The prevalence of the golden trait in some matrilines together with the available paternity data lent support to the matrilineal-specific mating model proposed by McMillan [McMillan, 1986; McMillan & Duggleby, 1981]. Additional paternity analyses will eventually prove or disprove this hypothesis.

Research interest in golden rhesus has focused on their use for studies of adult-onset macular degeneration (AMD) and glaucoma [Dawson et al., 2008] because their retinal pigmentary epithelial layer has reduced pigmentation and the choroidal

circulation and macula are, therefore, much more visible than in normal rhesus [Kessler et al., 1986].

Familial Circadian Rhythm Disorder

In humans, alterations of the circadian clock can lead to internal desynchrony between individual body rhythm or misalignment with a periodically changing environment, thereby increasing the risk for multiple disorders, including diabetes, obesity, heart disease, and eating disorders, such as night eating syndrome (NES) [e.g. Lewy, 2009; Maury et al., 2014; Rosenwasser, 2010]. The CS-derived group M monkeys at the SSFS were found to harbor the first known intrinsic circadian disorder in nonhuman primates [Zhdanova et al., 2012]. Monitoring entrained and intrinsic circadian rhythms of activity, food intake, and cognitive performance in 25 adult males and females (aged 5.5–27 years) from this group revealed a highly penetrant familial disease [see Zhdanova et al., 2016 this issue]. These findings provide novel opportunities for studying intrinsic circadian abnormalities homologous to human conditions.

DISCUSSION

This review summarized over 40 years of genetic research carried out on the CS rhesus macaque population, its derivative colonies and skeletal remains from either source. Spurred by the introduction of new genetic technologies, initiation of a systematic census and regular genotyping has enabled comprehensive investigations ranging from behavioral to functional and quantitative genetic studies.

With over 4,400 animals genotyped to date, the CS genetic database represents the most comprehensive resource of its kind for any free-ranging primate population. The genotypes that have accumulated over the years have facilitated both paternity assessment and confirmation of maternity inferred from behavioral observations of mother–infant pairs. This invaluable information has been used to reconstruct pedigrees comprising several generations, which together with the demographic data collected since 1956 enhanced the unique value of the CS colony for anthropological, behavioral, genetic, demographic, and biomedical research even further. The past and ongoing genetic work at CS both preceded and complemented that of The Rhesus Macaque Genome Sequencing and Analysis Consortium [Gibbs et al., 2007]. However, the studies at CS still stand out in that the colony is the least substructured (or "purest" in sense of little to no incoming post-migrational gene flow) rhesus population of Indian-origin kept anywhere in the US [Kanthaswamy et al., 2010].

The CS population is also unique in that it combines several advantages typical of captive populations with sufficient closeness to the natural situation in the wild. In contrast to captive studies, animals on CS (i) still search for natural food and are only partly provisioned, (ii) can avoid social interactions with challengers, (iii) can migrate to different social groups (males), and (iv) can choose mating partners freely (females). Furthermore, medical treatment is minimal. Hence, CS presents a natural population but at the same time has detailed demographic and genetic data available in addition to providing easy access to animal samples (both invasive and non-invasive). The CS colony has also yielded a plethora of behavioral data that are highly valuable despite the fact that the population lacks a few characteristics of most wild population (e.g., predation) likely to influence survival rates, secondary sex ratios, kin networks, and reproductive outcome. Given that the population size on CS needs to be kept under control, genetic analyses were also a key issue for colony management with a view to preserve genetic diversity. Overall, CS has proven to be a bridge between field and laboratory research, as well as between wild and captive studies. The genetic research has demonstrated how the CS population can address important issues in primatology, ranging from biomedical models of human disease to evolutionary questions about animal behavior.

One important venue of future primate genetics research will be the transition from STRs to SNPs as genetic markers owing to the higher throughput, lower mutation rate, and lower genotyping error rate of the latter [e.g. Hauser et al., 2011; Kanthaswamy et al., 2010]. For rhesus macaques, some millions of SNPs have already been identified in a few individuals [e.g., Kanthaswamy et al., 2013; Fawcett et al., 2011; Trask et al., 2011]. Once established for a given population, SNP typing is expected to provide more information more efficiently and at lower cost than STRs, even for degraded DNA [Phillips et al., 2008]. Although simulation studies have questioned the replacement of STRs by SNPs in kinship analysis [e.g. Amorim & Pereira, 2005], a recent hybridization study in macaques showed that a combination of both STRs and SNPs probably generates the most useful and reliable data compared to exclusively following one approach [Kanthaswamy et al., 2010]. In addition, a study on captive rhesus macaques suggested that a panel of 81 SNPs was as effective as the 14 highly polymorphic STRs to detect first-degree relationships, but that the STRs were more up to the task of distinguishing distantly related from all other relationships [Ross et al., 2014]. Nevertheless, if the identified SNPs were validated in a large number of individuals, this discrepancy may resolve and SNPs replace STRs as has happened in much of human genetics research [cf. Kim et al., 2010; Wei et al., 2012].

Another promising direction of future research on CS would be to use the colony as a model for more

human diseases, including age-related diseases. By means of high-throughput exome- or genome-wide sequencing [e.g., Vallender, 2011], genetic variants that contribute to relevant diseases could be identified efficiently in rhesus and point toward biological mechanisms underlying the human equivalent [cf. Rogers, 2013]. Whole genome sequencing of a small number of individuals is currently underway and will reveal the ease at which novel genetic variants can be detected in the CS population. However, greater possibilities will open up once a large number of animals have been sequenced.

Finally, the comprehensive genetic data available for the CS population provide an exceptional opportunity for quantitative genetic and evolutionary research. In particular, research questions related to the lifetime fitness of individual animals so far have been understudied in primates owing to their long generation time.

In summary, the rhesus macaques on CS have proven an invaluable resource for genetic and genetic-related research in the past. Nearly 100 publications bear witness to this fact. We hope that our review also serves to promote the future scientific use of the colony and of its invaluable combination of genetic, behavioral, and demographic data.

ACKNOWLEDGMENTS

We thank the staff of Cayo Santiago, especially Angel Figueroa and Edgar Davila, Chief Census Takers from 1973 to 1983 and from 1984 until present, respectively; Census Takers Julio Resto, Giselle Caraballo and Nahiri Rivera; and all former or current Scientists-in-Charge/Resident Scientists: Michael Tomilin, Rafael Luis Nieva, Jose Guillermo Frontera, Stuart Altmann, Carl Koford, John Kaufmann, Elizabeth Missakian, Marge Varley, Halsey Marsden, Steven Vessey, John Morrison, Andrew Wilson, Donald Sade, Richard Rawlins, Curt Busse, John Berard, Fred Bercovitch, Iris Velazquez, Melissa Gerald, Adaris Mas Rivera, and Angelina Ruiz-Lambides. Furthermore, we are grateful to all Colony Managers, investigators, veterinarians, veterinary technicians and assistants, especially Hector Martinez, and others who made contributions to the demographic data base. The authors also thank former CPRC Director Edmundo Kraiselburd and former CPRC Associate Director Janis Gonzalez-Martinez for their steadfast support during the past dozen years and Louis S. Harris for supporting graduate research on Cayo Santiago since 1998 through the Louis S. Harris Endowment to the University of Puerto Rico. We thank Constance Dubuc, Lauren Brent, Lars Kulik, Brigitte Weiß, Anthony Di Fiore, and two anonymous reviewers for fruitful discussion and comments on an earlier version of the manuscript and Mirjam Minkner for reference management support. The genetic studies were funded by the National Science Foundation (IBN 9209510 to FBB, SOC 7305516-01, SOC 39927-X00 to CD) and the German Research Foundation (DFG) (Nu 50/3-2, 6-1 to PN, Kr 1093/3-1, 5-2 to MK, Sa 661/1-1 to US, Schm 373/17-1 to JS; WI 1808/1-1, 1-2, 2-1, 3-1, 5-1 to AW). Currently, genotypes are generated in the Veterinary Genetics Laboratory at UC Davis, USA, the Max-Planck Institute for Evolutionary Anthropology and the University of Leipzig, Germany. The CPRC was supported during the period of these studies by the National Institutes of Health, National Center for Research Resources (contracts NIH-71-2003 and RR-7-2115; grants P40-RR-01293 and P40-RR-03640) and the Office of Research Infrastructure Programs (grant P40-OD-012217). The University of Puerto Rico provided partial support for the CPRC. Curation of the CPRC Skeletal Collection was partially supported by the National Science Foundation (NSF SBR-84-06541, HOMINID grant BCS0725183). The content of this article is solely the responsibility of the authors and does not necessarily represent the views of NIH, DRR, ORIP, DFG, or UPR.

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