Review

Evolutionary genetics in wild primates: combining genetic approaches with field studies of natural populations

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Ecological and evolutionary studies of wild primates hold important keys to understanding both the shared characteristics of primate biology and the genetic and phenotypic differences that make specific lineages, including our own, unique. Although complementary genetic research on nonhuman primates has long been of interest, recent technological and methodological advances now enable functional and population genetic studies in an unprecedented manner. In the past several years, novel genetic data sets have revealed new information about the demographic history of primate populations and the genetics of adaptively important traits. In combination with the rich history of behavioral, ecological, and physiological work on natural primate populations, genetic approaches promise to provide a compelling picture of primate evolution in the past and in the present day.

Genetic studies of natural primate populations

Our closest living relatives, the nonhuman primates, are perennial subjects of public and scientific fascination because they occupy a unique place in evolutionary biology and ecology. The striking similarities we share with other primates make them important models for human physiology, behavior, and health [1–4]. At the same time, variation among primate populations and species provides a rich basis for comparative work (e.g. Refs [5–7]). Such work is crucial for understanding the common threads that tie primates together and the differences that make specific branches of the primate tree, including the human lineage, unique.

Within the larger primate literature, studies that focus on wild primates offer a unique perspective on how ecological and environmental factors influence evolutionarily important traits. Indeed, primates are well represented among systems for which extensive field data are available, many of which are extremely fine-grained and some of which is continuous over multiple decades (Table 1). As a result, for many species we now know a great deal about the relationship between ecological and environmental variation, social structure, demography, and physiology. Together these types of data contribute to a rich understanding of how primates evolve.

By contrast, we know relatively less about the evolutionary genetics of wild primate populations. More so than for behavioral and ecological studies, research in this field has been constrained by the available technology. Thus, whereas observational methods for collecting behavioral data have remained relatively consistent over the past several decades, the possibilities for genetic analysis have only recently expanded from allozyme analyses of one or a few protein-coding loci, through analyses of modest microsatellite data sets, to the current ability to produce the kinds of large data sets amenable for highly powered population and functional genetic studies [8,9].

Primate studies are well positioned to take advantage of these new approaches. In particular, the increasing ease of genetic data collection (Figure 1) addresses one of the historical challenges of working on nonhuman primates. Already, the number of full genome sequences available for primates exceeds that for most other groups of animals [10], a testament to the importance of primate studies to the scientific community and to research relevant to human evolution and health. Meanwhile, the collection of phenotypic and environmental data remains a core strength of primate field studies. Such data act as an important scaffold for genetic studies, providing crucial ecological and behavioral insight into the causes and consequences of genetic patterns.

Here we consider the possibilities for integrating genetic data and analysis with the extensive field-based data sets on natural primate populations, drawing from recent examples in the literature (we focus on conceptual approaches for this integration; for a detailed review of methods for obtaining samples and molecular techniques useful in primate research, see Ref. [8]). This direction offers the opportunity to combine genetic, phenotypic, and environmental perspectives on the same individuals, an approach that has already proven instrumental for testing long-standing hypotheses in primate behavioral ecology (e.g. Refs [11–13]). Although some of the most exciting findings are undoubtedly yet to come, results from completed work already illustrate the potential of such studies for understanding the population and functional genetics of primate populations.

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Table 1. Primate genomic resources are complemented by long-term field studies

	Species	Representative long-term field studies	Website or representative publication [Ref.]	Genomic resources
Apes	Common chimpanzee (*Pan troglodytes*)	Bossou, Nimba Mountains, Guinea Budongo Forest, Uganda Gombe Stream National Park, Tanzania Mahale Mountains National Park, Tanzania Kanyawara, Kibale National Park, Uganda Ngogo, Kibale National Park, Uganda Taï National Park, Côte d'Ivoire	www.greenpassage.org culture.st-and.ac.uk/bcfs/index.html www.discoverchimpanzees.org [96] www.fas.harvard.edu/~kibale [97] www.eva.mpg.de/primat/files/chimps.htm	Genome sequenced
	Bonobo (*Pan paniscus*)	Lui Kotale, Salonga National Park, DRC Lomako Forest, DRC	www.eva.mpg.de/primat/files/bonobo.htm www.uoregon.edu/~fwhite/Lomako Forest Bonobo Project.htm	Genome sequence in progress
	Gorilla (*Gorilla gorilla* and *Gorilla beringei*)	Bwindi Impenetrable National Park, Uganda Karisoke, Virunga Mountains, Rwanda Mbeli Bai, Nouabalé-Ndoki National Park, Congo	www-rcf.usc.edu/~stanford/bigape.html www.gorillafund.org/conservation/karisoke_research_center.php [98]	Genome sequence in progress
	Orangutan (*Pongo* sp.)[c]	Gunung Palung National Park, Indonesia Ketambe, Indonesia; Kutai Game Reserve, Indonesia; Lower Kinabatangan, Indonesia; Suaq Balimbing, Indonesia; Tanjung Puting Reserve, Indonesia	people.bu.edu/orang [99] [99] [99] [99] [99]	Genome sequence in progress
	White-cheeked gibbon (*Nomascus leucogenys*)[d]			Genome sequence in progress
OW monkeys[a]	Baboon (*Papio* sp.)[e]	Amboseli National Park, Kenya Awash National Park, Ethiopia Cape Peninsula, South Africa De Hoop Nature Reserve, South Africa Drakensberg Mountains, South Africa Gashaka Gumti National Park, Nigeria Gombe Stream National Park, Tanzania Kafue National Park, Zambia Laikipia, Kenya Mikumi National Park, Tanzania Moremi Game Reserve, Botswana	www.princeton.edu/~baboon [81] www.baboonsonline.org/bru [100] [100] www.ucl.ac.uk/gashaka/home [101] [102] www.baboonsrus.com; www.rci.rutgers.edu/~palombit web.anglia.ac.uk/abru/info.htm www.psych.upenn.edu/~seyfarth/Baboon research/baboon.htm	Genome sequence in progress; genetic linkage map; ENCODE comparative sequence
	Vervet monkey (*Cercopithecus aethiops*)	Amboseli National Park, Kenya Samburu National Park, Kenya	[15] [103]	Genome sequence pending; genetic linkage map; ENCODE comparative sequence
	Long-tailed macaque[f] (*Macaca fascicularis*)	Ketambe River, Sumatra, Indonesia	[104]	Genome sequence in progress
	Rhesus macaque (*Macaca mulatta.*)	Cayo Santiago, Puerto Rico[g]	cprc.rcm.upr.edu	Genome sequence complete; genetic linkage map
	Eastern black and white colobus (*Colobus guereza*)	Kakamega Forest National Reserve, Kenya Kibale National Park, Uganda	[105] [106]	ENCODE comparative sequence
NW monkeys[b]	Owl monkey (*Aotus nancymaae*)[h]			ENCODE comparative sequence
	Common marmoset (*Callithrix jacchus*)	Tapacura, Brazil	[107]	Genome sequence in progress; ENCODE comparative sequence
	Squirrel monkey (*Saimiri* sp.)	Corcovado National Park, Costa Rica Manu National Park, Peru Raleighvallen National Park, Suriname	[108] [108] [109]	Genome sequence pending; ENCODE comparative sequence
	Dusky titi monkey (*Callicebus moloch*)	Manu National Park, Peru	[110]	ENCODE comparative sequence

Table 1 (*Continued*)

	Species	Representative long-term field studies	Website or representative publication [Ref.]	Genomic resources
Prosimians	Gray mouse lemur (*Microcebus murinus*)	Kirindy Forest, Madagascar	[111]	Genome sequence in progress; ENCODE comparative sequence
	Phillipine tarsier (*Tarsius syrichta*)	Corella, Bohol, Phillipines[i]	www.tarsiusproject.org	Genome sequence in progress
	Greater bushbaby (*Otolemur garnettii*)	Gedi National Monument, Kenya	[112]	Genome sequence in progress; ENCODE comparative sequence

[a]Old World monkeys
[b]New World monkeys
[c]Field studies of both Bornean and Sumatran orangutans (variably considered species or subspecies of a single species, *Pongo pygmaeus*) are included here.
[d]Other gibbon species are better studied in the wild (e.g. the agile gibbon, *Hylobates agilis* at Gunung Palung National Park, Indonesia [113]; the white-handed gibbon, *Hylobates lar*, and the siamang, *Hylobates syndactylus*, at Ketambe River, Indonesia [114]; and the white-handed gibbon at Khao Yai, Thailand [115])
[e]Field studies of several allotaxa of *Papio* are listed here, including those focused on hybrids. Some taxonomies consider these allotaxa separate species, and others as subspecies designations of a single species, *Papio hamadryas*. Genomic resource development has focused primarily on anubis baboons.
[f]Synonymous with crab-eating macaque or cynomolgus monkey.
[g]The Cayo Santiago rhesus macaque population is free-ranging, but not natural (rhesus macaques are native to Asia, not the Americas).
[h]Other *Aotus* species are better studied in the wild (e.g. the night monkey, *Aotus trivirgatus*, in Manu National Park, Peru [110]; Azara's night monkey, *Aotus azarae*, in Estancia Guaycolec, Argentina: see www.sas.upenn.edu/~eduardof/EstanciaGuaycolec.html).
[i]Unlike most of the other projects listed here, this is a shorter-term study focused primarily on data collection via radio telemetry (tarsiers are nocturnal).

Population structure and gene flow in a behavioral and ecological context

A central project of evolutionary geneticists focuses on understanding population history and demography. These are in turn mediated by individual dispersal patterns and differential reproductive success – parameters that have also been of great interest to primate field researchers. In particular, research on natural primate populations has focused intensively on the behavioral and ecological factors that contribute to variation in these characteristics (e.g. Refs [14–16]). Placing genetic data and inference in the context of this work therefore presents the opportunity to link changes in the genetic composition of a population with its proximate causes and resulting phenotypic effects.

In many primates, natural populations are subdivided into stable social groups. The size and composition of such groups vary within and between species, as do the patterns of dispersal that produce change in group membership over time [17]. In many cases, sex-biased dispersal (in which one sex typically disperses while the other remains in the natal group; this pattern can leave distinctive marks on different parts of the genome [18]) results in outbred social groups in which many individuals are nonetheless closely related and form tight social bonds [19]. This pattern closely matches the 'breeding group' model developed to account for the population genetic properties of species organized into stable social groups that also exhibit sex-biased dispersal and reproductive skew [20,21]. Because these properties (for example, co-residency of close, but not inbred, relatives within a social group) are likely to be important for the evolution of kin-biased behavior, they have also been of great interest to behavioral field biologists.

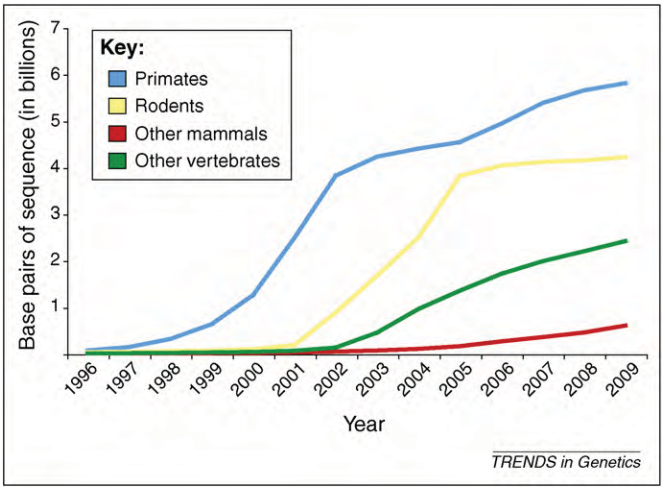

Figure 1. The amount of sequence data for primates has rapidly expanded. The availability of sequence-based resources sets the stage for work that integrates genetic perspectives with ecological, behavioral, and demographic data on the same species. Other groups (one other mammalian order, rodents; all non-primate, non-rodent mammals; and all non-mammalian vertebrates) are shown for comparison. Data reflect the amount of sequence data available at the end of each calendar year (in the December 15 yearly Genbank release), and were downloaded from NCBI (ftp.ncbi.nih.gov/genbank/release.notes/) on March 1, 2010.

The results of this work have provided deeper resolution into the kinds of behavioral variation that influence population structure. Indeed, studies in primates (in addition to other taxa; see for example Refs [22–24]) have highlighted how behavioral patterns can directly predict population genetic structure, thus providing a mechanistic explanation for the patterns embedded in genetic data. For instance, genetic structure in wild baboons (*Papio cynocephalus*) closely matches predictions arising from observational data on mate-guarding and dominance rank, emphasizing the importance of male reproductive skew in shaping population structure in this species [25]. Similarly, the values of classical F statistics (which evaluate the proportion of genetic variance in a population explained by subgroups within the population) in Venezuelan red howler monkeys (*Alouatta seniculus*) can be directly interpreted in the light of levels of reproductive skew, female philopatry, and male dispersal known from years of intensive field observations [26].

Social behavior and the structure of social groups can in turn be influenced by the spatial distribution of resources and local ecological and environmental patterns, a relationship that forms the core of the socioecological model for primate behavioral ecology [27,28]. Ecological

and behavioral data were key, for example, in understanding patterns of population structure in the eastern mountain gorilla (*Gorilla beringei beringei*) population of the Bwindi Impenetrable Forest in Uganda [29]. Among the Bwindi gorillas, population structure emerges primarily from the distribution of breeding females; males exhibit almost no discernible population structure. This sex difference occurs despite the fact that both male and female gorillas can disperse from their natal groups and the fact that female gorillas travel substantial distances in daily life. Ecological data on spatial variation in plant community composition revealed that females, but not males, express a behavioral preference for remaining in areas where the plant community is familiar [29]. Thus, local ecology exerts an important effect on the distribution of genetic variation in this population via sex differences in foraging behavior. This effect might also help to explain genetic data that indicate male-mediated historical gene flow between eastern gorillas and western gorillas [30,31]. If the patterns in Bwindi also held for gorilla populations in the past, primarily male-mediated gene flow between these species might have resulted in part from female preferences to maintain closer ties to a known resource base. Hence, ecological and behavioral studies of modern primate populations can aid in interpreting past population history, especially for species for which extensive population genetic analyses are also available [31–35] (Box 1).

Finally, field data can highlight the sensitivity of population structure to behavioral and demographic change. For instance, a long-term study of red deer (*Cervus elaphus*) showed that decreasing levels of observed population structure among females probably resulted from a decrease in reproductive skew (a behavioral pattern) caused by rapid recent population growth (a demographic effect) [24]. Similar kinds of data are available for many natural primate populations, making it possible to connect estimates of population genetic change with the underlying behavioral processes that generate it [36,37]. Such studies can illustrate how behavioral variation among individuals and behavioral plasticity within individuals – hallmarks of many primates – can influence the maintenance and distribution of genetic variation within populations (and also between populations and species in the more extreme case of hybridization: Box 2).

Box 1. Genetic data and demographic history in *Pan*

Genetic data carry the signature of past demographic events for many generations. Thus, they can make an important contribution to understanding historical population structure, growth, and change, and this in turn provides valuable context for genetic studies of field populations in the present. The power of genetic analysis in reconstructing the past is illustrated by the extensive genetic investigations of population history in chimpanzees and bonobos [32–34,76–78].

These studies demonstrate the nature of the insights that can be drawn from both modestly-sized multilocus studies and from more recent genome-scale studies. Encouragingly, inferences from these studies have been qualitatively consistent even across different data sets. For example, a recent large resequencing data set dated the divergence time between chimpanzees and bonobos at 1.29 million years [33], consistent with previous estimates (~0.8–1.8 million years [77,78]) but with a much smaller window of uncertainty. Smaller data sets have also suggested hypotheses that can be tested further. For example, a survey of nine unlinked intergenic regions revealed an excess of rare alleles relative to neutral expectations in central chimpanzees, a pattern suggestive of recent population expansion [77]. Indeed, a more recent analysis indicates that the effective population size of central chimpanzees has increased by at least four-fold since the split between central and western chimpanzees, whereas the western chimpanzee population has contracted during the same time [33].

Genetic data have also produced a better understanding of gene flow in chimpanzees. Both PCA and STRUCTURE analyses support the genetic distinctness of bonobos from chimpanzees and of chimpanzee subspecies from one another [32]. However, several studies also indicate past gene flow between western chimpanzees and central chimpanzees [33,76,79]. Thus, an isolation and migration model might better describe the demographic history of these groups than a simple split. One interesting possibility is that this link might have been enabled by the proposed fourth subspecies of chimpanzee, *P. t. vellerosus*, which could be genetically more similar to western chimpanzees but is geographically closer to central chimpanzees [79].

Taken together, work on the demographic history of chimpanzees provides a template for expanding genetic inference of demographic history in other primates. In addition, recent work illustrates how powerful inferences can be drawn from relatively small numbers of individuals, given large amounts of sequence data [33]. Data sets of these dimensions are readily generated through new sequencing technologies, and will be increasingly available in the near future.

Testing the selective import of functional variation

The action of natural selection on functional genetic variants (i.e. polymorphisms that have a causal relationship with trait variation) is responsible for much of the phenotypic diversity in behavior, physiology, and morphology exhibited by primates, including traits that differentiate humans from other primates. Identifying loci that have been targets of natural selection via sequence analysis is therefore a vital area of research in primate genetics. However, even when a locus is strongly marked by natural selection, understanding the reasons underlying its selective history can be greatly enhanced by studying its role within a natural ecological context (particularly in cases in which selection is thought to be strong). Combining sequence-based evidence for selection with phenotypic observations in the field therefore represents a natural integration of genetics, ecology, and behavior in wild populations.

This approach is nicely illustrated by work on the adaptive significance of trichromacy (i.e. full color vision). Despite the long history of research on color vision in primates, the selective advantage(s) of trichromacy continue to be the subject of debate [38–40]. 'Allelic trichromacy,' in which individuals within a species can be either dichromatic (red–green colorblind) or trichromatic depending on genotype, presents an opportunity to study the role of different visual systems in a natural ecological setting. Indeed, sequence-based analyses already support a role for natural selection in maintaining the polymorphisms responsible for variation in visual system [41,42], and the functional effects of the variants themselves are well characterized. The signature of selection in sequence data alone, however, is compatible with several different selective mechanisms, including heterozygote advantage, frequency-dependent selection, and niche differentiation by genotype.

Box 2. Genetic and phenotypic analyses of hybridization in primates

Genetic analyses and field observations can be merged to study an extreme case of gene flow – naturally occurring hybridization between primate species. Hybridization is a common phenomenon among primates, and has been proposed to play an important role in the evolution of the primate lineage [80]. Studying hybridization in wild primates is therefore of great interest for investigating the emergence of genetic and phenotypic differences between divergent groups.

Phenotypic data and genetic estimates of admixture can be combined, for instance, to investigate how hybridization influences fitness-related traits. In baboons (genus *Papio*), naturally occurring hybridization occurs at the geographic boundaries between all five species. Long-term observations in a hybrid zone in Ethiopia between anubis baboons (*P. anubis*) and hamadryas baboons (*P. hamadryas*) [81] suggest that behavioral prezygotic isolation does not play a strong role in checking this process, despite the markedly different social structures that characterize these two species. Although hybrid males are less likely to gain mates in some groups, they do equally as well as other males in groups that include many hybrids [82]. In Kenya, where yellow baboons (*P. cynocephalus*) and anubis baboons sometimes hybridize, genetic and phenotypic data suggest that hybrids might in fact enjoy a fitness advantage [36,37]. More anubis-like individuals mature earlier, especially males [36]; anubis-like males also appear to be more successful in competing for mates (J.T, S.C.A. and J. Altmann, unpublished data). These data contrast sharply with work on hybridization in New World howler monkeys. Although mantled howler monkeys (*Alouatta palliata*) and black howler monkeys (*A. pigra*) naturally hybridize where their ranges overlap in Mexico, observational and genetic evidence suggest that only female hybrids are viable and fertile [83]. This case represents perhaps the best evidence for the accumulation of intrinsic postzygotic isolation in naturally hybridizing primates, suggesting fertile ground for comparison between cases of hybridization across different primate taxa.

Future work on these systems will be able to both investigate how genetic background correlates with interesting traits, and will attempt to identify the loci responsible for phenotypic differences between hybridizing species. Admixture mapping approaches, which investigate how ancestry-informative genetic markers and trait variation cosegregate among admixed individuals, will be particularly appropriate for this line of work [84]. Additionally, increasing amounts of genetic data on hybridizing populations will enable investigators to complement data on hybridization in the present with estimates of the timing and rate of gene flow between species in the past.

Field studies provide a way to test these alternative hypotheses. In these studies, genotypic information on functional opsin variation is integrated with phenotypic information on individual behavior collected under natural conditions. For example, one prediction of a heteroyzygote advantage hypothesis is that heterozygous individuals exhibit an overall foraging advantage relative to homozygotes (all trichromatic individuals are heterozygotes in these species; homozygotes are dichromatic). However, when tested in the field, no general trichromat advantage has been identified for either wild spider monkeys (*Ateles geoffroyi*) [43] or wild white-faced capuchins (*Cebus capucinus*) [44]. Alternatively, a niche differentiation hypothesis predicts that dichromats and trichromats will excel at different kinds of foraging tasks. Indeed, in capuchins, dichromats detect camouflaged insects better in low light, whereas trichromats enjoy an advantage in obtaining embedded, noncryptic insects [45], although they do not spend different amounts of time feeding on specific resources [46]. These studies have thus made early inroads into understanding the selective import of different visual systems in natural populations. Comparative work across other species that exhibit allelic trichromacy (most New World monkeys and several lemurs), but that experience different ecological circumstances, should shed further light on these questions.

Thus, field data can help fill in even a well-studied evolutionary picture by providing a testing ground for investigating how genetically different individuals differ phenotypically in the wild. In cases where similar functional genetic variants segregate in both humans and nonhuman primates, they can also shed light on our own evolutionary past. For example, both humans and chimpanzees (*Pan troglodytes*) harbor genetic variation at the *TAS2R38* gene which alters individual sensitivity to bitter-tasting compounds [47], and which appears to have evolved under selection in humans [48]. Studying the proximate impetus for natural selection on human populations is difficult, given the dramatic changes in the human diet from ancient to modern times. The parallel relationship in chimpanzees, however, presents the opportunity to study how similar variants influence dietary choices in a natural context in our closest living relatives (although the selective regime on *TAS2R38* in chimpanzees probably differed from that in humans [47]).

Functional genetics and the genotype–phenotype relationship in wild primates

One of the most exciting possibilities for genetic research in natural primate populations lies in the prospect of identifying functional genetic variation that influences ecologically and adaptively relevant traits (Box 3). This area of research is in the early phase of development. Indeed, the genome-scale approaches that will probably move this area forward have, until recently, been impracticable in wild primates. Thus, functional studies in primates have largely relied on candidate gene approaches motivated by existing information on humans, and genotype–phenotype mapping studies have largely been confined to captive animals (Box 4). However, even at this modest scale, several of the unique contributions that arise from combining genetic approaches with behaviorally and ecologically well-studied populations are already apparent.

First, field studies enable research into traits that might not be relevant or variable in captive primates, but are important in natural populations and are relevant to human health and disease. Wild primates are subject to naturally occurring infection by a wide variety of parasites and pathogens that do not occur in captive colonies. Simian immunodeficiency virus (SIV) is both common and highly pathogenic in the wild chimpanzee population of Gombe National Park, for example, but had previously been thought to be rare and nonpathogenic based on studies in captive chimps [49]. In such cases, field data are crucial to understanding genetic variation that influences trait variation. For instance, like humans, nonhuman primates act as hosts for the group of parasites that cause malaria in humans. Indeed, in several cases, these parasites have been shown to cross-infect across multiple primate species (*Plasmodium falciparum*, for instance, has been shown to infect wild chimpanzees as well as

Box 3. Why conduct functional genetic research in wild primates?

To date, most functional genetic studies in primates have been conducted in a captive or laboratory setting, where individual subjects can be manipulated and *in vitro* tools (such as luciferase reporter assays in cell culture) can be exploited. However, although these approaches are of great value, they are also limited. *In vitro* effects do not always recapitulate *in vivo* biology [85], and a functional effect identified *in vitro* might not be relevant to animals in their natural environment. Gene–environment interactions, in which functional genetic effects change in direction or magnitude across environmental conditions, can also confound attempts to extrapolate from the laboratory to natural populations. In addition, captivity itself can produce artifacts, particularly in stress and immune-related pathways [86].

These factors strongly argue for inclusion of individuals sampled under natural conditions in functional genetic studies, and the most obvious choice for such work are systems for which observational field data are readily available. Genetic work on these populations comes with some natural advantages. In particular, they bring to the table a wealth of existing knowledge about the distribution of phenotypic variation, the distribution of ecological and environmental variation that individuals within the sample experience, and the relationship between these two factors. Given that phenotypic variation is classically modeled as the result of a combination of environmental factors, genetic factors, and the dependent interactions between them [87], this means that several major parts of the overall picture are already in place. Indeed, recent trait-mapping work in human genetics suggests that incorporating environmental effects in genotype–phenotype modeling can improve the ability to detect genetic associations [88]. Finally, these data also position natural primate populations as good models for studying the evolutionary relevance of genotype–environment interactions.

Furthermore, natural primate populations provide a unique window into human biology and evolution. Unlike studies in modern human populations, behavioral and demographic observations of nonhuman primates occur in real-time and can be extremely fine-grained (in some cases, occurring on a near-daily basis). Nonhuman primates are therefore particularly well suited for certain kinds of studies, including longitudinal studies of maturation and aging [5], and studies that investigate the relationship between genetic effects and sociosexual behaviors. Because the ecological circumstances of nonhuman primates have not changed over time as dramatically as they have for modern humans, they also allow researchers to interrogate the selective effects of genetic variation in an environment more similar to that in which it evolved.

Box 4. Captive primate populations

Although the goals of research on captive primates often differ from the goals of work on natural populations, the availability of large research communities that work in both milieus creates the opportunity for collaboration and interplay between research done in captive settings and in the wild. This can take at least three forms:

Resource development. Because of the strong biomedical focus of many captive primate facilities, development of genetic resources has been a priority for species that are medical models for human disease. These priorities have influenced both major institutional priorities, such as the choice of genome sequencing targets, and also the generation of additional resources, especially genome-wide linkage maps [89–91]. These markers often translate well between captive and natural populations. As marker development becomes a greater priority for field populations as well, this exchange of resources is likely to accelerate and become increasingly bidirectional.

Hypothesis generation and an alternative testing arena. Studies in captivity can be important for providing the first tests of ecological and evolutionary hypotheses. For example, foraging tasks set for captive animals have been key to understanding the selective maintenance of allelic trichromacy (e.g. Refs [92,93]). In other cases, work on captive animals has focused on phenotypes or environments that are less obviously relevant to evolution in natural populations. Captive studies in rhesus macaques, for instance, have delved into the genetic and environmental basis for alcoholism and for aggressive behavior in animals reared by peers [1]. Although these tests are not obviously mirrored by naturally occurring situations, they have identified genetic variants and broad environmental categories that motivate research on other traits with a potentially shared mechanistic basis (e.g. Ref. [62]).

Replication. In nonhuman primates, sample sizes for genetic studies will generally be relatively small. Where possible, the existence of both captive and wild populations for a given species can be leveraged to test replication of apparent genetic effects (although some caveats attach to such comparisons: see Box 3). For example, hybridization between yellow baboons and anubis baboons is known to influence morphological traits in the wild [94]. A QTL mapping study in captive baboons (a colony that also includes anubis-yellow hybrids) has identified candidate regions of the genome that influence morphological variation [95], providing insight into the possible basis for this effect. As the genetic basis for such traits becomes more clear, checking for consistency between multiple populations should therefore be of considerable interest.

humans: [50]) or have undergone evolutionary transitions to move from nonhuman primates to humans [51]. However, little is known about how genetic variation in wild primates influences risk of infection. Baboon populations in east Africa exhibit high rates of natural infection by *Hepatocystis kochi*, a parasite nested within the primate *Plasmodium* clade, offering an opportunity to pursue such work [52]. Indeed, recent evidence supports a link between *Hepatocystis* susceptibility in wild baboons and genetic variation at the baboon Duffy antigen receptor for chemokines (*DARC*; also abbreviated *FY*) that also influences gene expression of the baboon *DARC* gene *in vivo* [53]. This association parallels the known link in humans between *DARC* genetic variation and infection by the malarial parasite *Plasmodium vivax*, an effect mediated by variation in *DARC* gene expression [54,55]. Other disease-related traits might be influenced by similar parallelisms. For example, copy-number variation at the chemokine (C-C motif) ligand 3-like (*CCL3L*) locus has been linked in some studies to HIV or SIV progression in humans [56] and in captive rhesus macaques (*Macaca mulatta*) [57]. Segregating copy-number variation at *CCL3L* is also found in chimpanzees [56,57], and represents a potential target for such work.

Second, field data are necessary to understand the role of functional genetic variation in natural populations, even when the genetic variants are well studied in captive animals. For example, the serotonin transporter gene, *SLC6A4*, encodes a protein that plays an important part in controlling circulating serotonin concentration. Like humans, rhesus macaques harbor segregating genetic variation in both the promoter and the 3' untranslated region of this gene that influence levels of *SLC6A4* expression [58–60] and cerebrospinal fluid serotonin metabolites [58]. Because levels of these metabolites, especially 5-hydroxyindoleacetic acid (5-HIAA), have been linked with natal dispersal timing in free-ranging male rhesus macaques [61], genetic variation in *SLC6A4* was also hypothesized to associate with differences in male dispersal timing. Indeed, a functional promoter variant at this locus

significantly associates with timing of male natal dispersal (the low-expressing allele is linked to delayed dispersal [62]) and, perhaps because of the dispersal effect, with timing of male reproduction [63]. This example highlights the type of trait that will be of particular interest for primate field studies: even though dispersal timing is impossible to study in the laboratory, it is an important fitness-related trait in many primates, and one that has been extensively studied in natural populations [19].

What lies ahead for the genetics of natural primate populations?

Field-based ecological, behavioral, and demographic data already play an important role in genetic studies of nonhuman primates, and will be increasingly important in the future as the scope and scale of genetic data on wild primates grow. Recent technological and methodological advances, especially high-throughput sequencing approaches, represent a major advance for the field. Indeed, the extensive data collection these tools enable mean that, for the first time, the quality and quantity of genetic data on wild primates will complement the rich behavioral and ecological data sets already in place for many of these species. This expansion of the available data will undoubtedly have dramatic consequences for studies of primate genetics, and we outline some of the possibilities below.

Novel data sets for resource development and genomic exploration.

As a direct consequence of the falling cost of genomic technologies, population-based data collection is becoming increasingly feasible to conduct, even for non-model organisms. As a result, individual investigators are now able to collect large genetic data sets tailored to their specific species and/or study populations, at a much more rapid rate than in the past. This development will not only lead to a vast increase in the availability of genetic markers, but will also allow primate evolutionary geneticists to explore aspects of genome function that go beyond variation at the sequence level (including quantitative measurements of gene expression, epigenetic patterns, protein–DNA binding, and copy number variation [64]), particularly for tissues that are often feasible to sample in the field, such as skin and blood (see also 'Challenges'). Conducting such assays on a genome-wide level will allow investigators to ask how change at the genome sequence level translates into change in genome function, including at adaptively relevant traits. This research question is already being addressed in interspecific comparisons between humans, chimpanzees, and rhesus macaques (the primates that currently boast the highest-quality genome sequence) [65,66]. However, we still know very little about intraspecific variation in genome structure and function in primates, including how variation is partitioned among populations that are exposed to different ecological regimes (a major area of research in human genetics, but for which no comparative data in other primates currently exist). We anticipate that the next several years will witness a vast expansion in the data sets needed to address these questions.

Population history and demography

Previous studies have provided important insights into demographic processes such as admixture and gene flow [18]. New waves of genetic data are positioned to build on this work by providing much more fine-grained estimates of these processes. These results will eventually allow us to investigate, for example, how and why the evolutionary histories of species that experienced similar patterns of historic environmental change might have differed. Genetic data can also be combined with high-resolution geographic information system (GIS) data to understand how features of the environment affect the distribution of genetic variation in modern populations (part of the emerging field of landscape genetics [67]). Such analyses can be leveraged both to understand the behavioral and ecological determinants of population structure in the present, and to help interpret the possible role of ecological and environmental factors that influenced genetic exchange in the more distant past. Studies with relatively limited genetic data sets have already revealed clues to how anthropogenic environmental change has influenced the distribution of several endangered primates [68,69]. With the greater power provided by larger data sets, these analyses will soon become generalizable to a larger number of systems and will be accompanied by improved inference into relationship between geographic variation and population history.

Functional genetics and the genotype–phenotype relationship

Trait-mapping studies will also be able to take advantage of larger-scale genotyping and resequencing data sets. For candidate gene studies, these approaches will provide much improved ability to correct for potential confounds, such as cryptic population structure and relatedness. Even more importantly, they will allow the field to expand its perspective beyond candidate genes to investigate previously uncharacterized loci. These studies will help address, for instance, the degree to which parallel genotype–phenotype relationships between species (broadly defined here as functional genetic variants at homologous loci, which influence the same or similar phenotypes: [47,53,57,62,70]) relate to shared ancestral selection pressures. Finally, genetic studies will be able to better exploit the historic strengths of primate field research: individual-centered environmental and phenotypic data collection over the life course. For example, early-life effects play an important role in influencing phenotypic variation in humans and in nonhuman primates [71–74]. The ability to scan the genome for environmentally-induced epigenetic modifications presents a new opportunity to understand the possible mechanisms connecting early life with trait variation later in life.

Challenges

A central theme of this review is to emphasize how new technological and methodological developments are making it increasingly possible to conduct genetic studies in natural primate populations, where genetic inferences can be combined with behavioral, ecological, and other sources of data. Although these developments are unquestionably

expanding the possibilities for research in primate genetics, some important challenges remain.

First, and especially for collection of genomic data sets other than sequence or genotyping data, obtaining tissue samples from wild primates will often be very difficult (especially for some tissue types of great interest, such as brain or liver). Thus, the first waves of analysis will probably focus on sample types that are easier to obtain, such as blood, skin, or samples suitable for microbiome analysis (fecal samples or vaginal, buccal, or nasal swabs); field studies have already proven adept at gathering such samples from a variety of primates (e.g. Refs [25,75]). Opportunistic sampling from natural deaths can also serve as a strategy for building up sample sets over time (akin to strategies for recovering tissues from zoo primates), although such opportunities will be rare. Although these approaches will not give us a comprehensive look at all aspects of genetic and genomic variation, research in humans has demonstrated that we can learn a great deal from blood cells alone (all the HapMap cell lines, for example, are lymphocytes). Such samples are also highly relevant for a major focus of primate research, the evolution of the immune system and disease resistance. With optimization, the new generation of genomic tools might also become applicable to noninvasively collected samples such as shed hair and feces, greatly expanding the possibilities for population-based research.

Second, dissecting genotype–phenotype relationships remains a major challenge across all organisms, including in humans and in model systems. Even in the most extensively studied nonhuman primates, long life-histories and relatively low densities mean that sample sizes will probably remain modest. This area invites collaboration between researchers working on different populations, including those focused on captive populations (Box 4). Investigators interested in pursuing trait associations will also often need to include alternative sources of information – particularly about the mechanisms through which genetic effects act – into genotype–phenotype mapping studies. Indeed, in the examples of genotype–phenotype studies published thus far in primates, *in vitro* functional tests and *in vivo* measurements of molecular intermediaries such as gene expression have bolstered the overall case for a genotype–phenotype relationship.

Finally, much of this work will rely extensively on computational and statistical modeling skills, in addition to expertise in field research, behavior, and ecology. Developing skills in statistics and programming will therefore be an important training priority. Taking account of population and species-level characteristics in analyses of large-scale data sets will therefore require substantial investment in developing models appropriate for each individual system.

Conclusions

Genetic studies in primates present the exciting possibility that genetic inferences can be placed in the context of complementary behavioral and ecological data about the same systems, gathered under natural conditions. This opportunity has been made possible by generations of primate field research. These efforts have produced a well-developed framework for understanding the causes and consequences of genetic evolution. As genomic resources for these species proliferate, natural primate populations will become increasingly good subjects for evolutionary genetics research. This area of research therefore has the potential to spur remarkable new collaborations that bridge lab-based molecular genetics, computational modeling and data analysis, and field-based data collection on natural populations.

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