Great Ape Genomics

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Abstract

The great ape families are the species most closely related to our own, comprising chimpanzees, bonobos, gorillas, and orangutans. They live exclusively in tropical rainforests in Central Africa and the islands of Southeast Asia. Due to their close evolutionary relationship with humans, great apes share many cognitive, physiological, and morphological similarities with humans. The members of the great ape family make obvious models to facilitate the further understanding about humans' biology and history. This review will discuss how the recent addition of genome-wide data from great apes has furthered humans' understanding of these species and humanity, especially in the realm of evolutionary genetics.

Key Words: conservation genetics; demography; evolution; great apes; natural selection; population size

Introduction

It has long been hypothesized that humans and the great apes share a recent common ancestry (Huxley 1863; Darwin 1871). This result has been confirmed by many molecular studies over the past several decades (Sibley and Ahlquist 1987; Goodman 1996; Satta et al. 2000; Chen and Li 2001). It is now known that common chimpanzees (*Pan troglodytes*) and bonobos (*Pan paniscus*) are our closest living relatives, followed by gorillas and orangutans (Figure 1). The sequence divergence at orthologous sites between humans and chimpanzees/bonobos is just 1.2% (Chimpanzee Sequencing and Analysis Consortium 2005; Prufer et al. 2012), which is much less than the divergence between two random fruit flies (*Drosophila simulans*) of the same species (Begun et al. 2007). Great apes are studied by geneticists for a wide variety of reasons, including intrinsic biological interest, interest in the horizontal transfer of pathogens such as HIV-1 (Keele et al. 2006), implications for conservation

biology, and interest in recently evolved human-specific traits such as bipedality and large, complex brains. With assembled genome sequences now available from four different great ape species (Chimpanzee Sequencing and Analysis Consortium 2005; Locke et al. 2011; Prufer et al. 2012; Scally et al. 2012), as well as 100 additional genomes available for population genomic studies (Locke et al. 2011; Auton et al. 2012; Prado-Martinez et al. 2013), there is now an unprecedented ability to study the evolution of humanity's closest relatives. This review highlights how recent comparative studies have enhanced the knowledge of human genetics and human evolution. A comprehensive review is beyond the scope of this paper; rather, it highlights specific topics that represent major areas of current research.

How Are Humans Unique?

By aligning the human reference sequence to the genomes of several closely related outgroup species, we can identify mutations that have occurred on the recent human branch and distinguish between ancestral and derived alleles at human single nucleotide polymorphisms (SNPs). Over the whole genome, these mutations occur at a roughly constant rate, consistent with the idea that the vast majority of substitutions are selectively neutral (i.e., nonfunctional) (Kimura 1983). Orangutans with a 2.4-fold higher sequence divergence (compared with chimpanzees) are expected to have a 2.4-fold longer divergence time from humans, in relation to the human-chimpanzee divergence time (Figure 1). Part of the challenge of identifying the genetic basis of human-specific morphological change is the difficulty in distinguishing between rare functional mutations and the more common selectively neutral mutations that separate humans from the great apes. For obvious ethical reasons, function can generally not be inferred in vivo. Rather, indirect computational techniques, as well as the utilization of a more distantly related animal model (e.g., mice and fruit flies) have been used to identify human-specific adaptations.

Coding Changes

One approach for identifying human-specific adaptions is to scan the exomes of humans (and various outgroups) to identify genes with patterns of genetic variation that are consistent
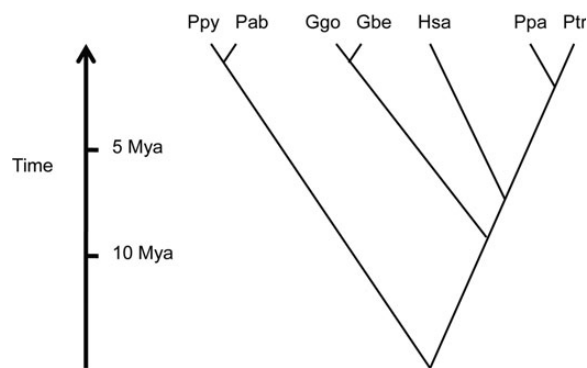
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Figure 1. Schematic showing the evolutionary relationships and approximate divergence times among the great apes and humans. Ppy, *Pongo pygmaeus*; Pab, *P. abelii*; Ggo, *Gorilla gorilla*; Gbe, *G. beringei*; Hsa, *Homo sapiens*; Ppa, *Pan paniscus*; Ptr, *P. troglodytes*; Mya, Million years ago.

with the action of recent natural selection. For example, Enard and colleagues (Enard et al. 2002) sequenced the FOXP2 gene, a forkhead class transcription factor, in humans, great apes, and mice. The gene is highly conserved among mammals, with just one non-synonymous (i.e., amino-acid changing) mutation separating the chimpanzee and mouse coding sequences. This conservation is not due to a low mutation rate, as there are 147 synonymous (i.e., non-amino acid changing) mutations between chimpanzees and mice. However, on the human-specific branch, there are two non-synonymous mutations and no synonymous mutations, which is significantly different from expectations ($p < 10^{-3}$, Fisher's exact test). Enard and colleagues interpreted this (and other evidence) as support for recent positive selection in the human lineage (Enard et al. 2002). Since mutations in FOXP2 can cause deficiencies in spoken language capacity, Enard and cohort speculated that the non-synonymous mutations in FOXP2 were related to humans' ability to develop complex forms of communication. Subsequent work has shown that both Neanderthals and Denisovans also contain these two recent non-synonymous mutations (Krause et al. 2007; Reich et al. 2010), though this observation can be interpreted in different ways (Coop et al. 2008; Ptak et al. 2009). Recent work has suggested that a mutation at a transcription factor binding site in intron 8 of the FOXP2 gene affects FOXP2 expression levels. These expression levels might have been recently selected for because they differ between modern humans and Neanderthals (Maricic et al. 2012).

Subsequently, researchers have searched more systematically through many different genes to look for a similar signal of increased human-specific, non-synonymous substitutions relative to synonymous substitutions; first using unrooted trees (Clark et al. 2003; Nielsen et al. 2005) and later with one or more outgroups (Rhesus Macaque Genome Sequencing and Analysis Consortium 2007; Lindblad-Toh et al. 2011). These studies have identified functional categories (i.e., the genes involved in spermatogenesis) that are enriched in genes showing evidence for positive selection, but the biological insight gained from these broad surveys is

somewhat limited. Deeper insight generally requires additional information from physiological, behavioral, or targeted genetic studies. For example, great ape species differ in the size and structure of their social groups—chimpanzees live in multi-male, multi-female groups; gorillas live in single male, multi-female groups; and orangutans are mostly solitary. These life-history traits suggest that different great ape species undergo different sexual selection pressures. In particular, since receptive chimpanzee females mate with multiple males (unlike gorilla and orangutan females), it is expected that sperm competition will be more important for chimpanzee males than for males of other great ape species. Both physiological (Harcourt et al. 1981) and genetic (Dorus et al. 2004) studies provide support for this hypothesis, and may provide a partial explanation for the prevalence of genes that are involved in spermatogenesis that appear to be affected by recent positive selection.

Another approach for detecting the action of recent natural selection on the human lineage involves comparing synonymous (i.e., non-amino-acid changing) versus non-synonymous (i.e., amino-acid changing) polymorphisms and substitutions. If a gene has been subject to recent positive (i.e., adaptive) selection, this can lead to the fixation of several non-synonymous mutations, and an excess of non-synonymous substitutions relative to non-synonymous polymorphisms (McDonald and Kreitman 1991). Conversely, under continued purifying selection most non-synonymous mutations will be deleterious, and very few will rise in frequency to become fixed differences. This will tend to produce a deficit of non-synonymous substitutions relative to non-synonymous polymorphisms. Bustamante and colleagues examined the patterns of polymorphism and divergence in thirty-nine humans (20 European-Americans and 19 African-Americans) and one chimpanzee at more than 11,000 different protein-coding genes (Bustamante et al. 2005). As with other studies, they found certain functional categories were overrepresented (or underrepresented) among genes that they had inferred to be recently selected for, but functional insight for specific genes was minimal.

Regulatory Changes

One potential limitation of the studies described above is that they are confined to protein-coding regions, which comprise <2% of the human genome. It is possible that most of the genetic changes that "make us human" involve regulatory sequences rather than coding sequences (King and Wilson 1975). To identify the noncoding regions that are important to recent human evolution, Pollard, Siepel, and colleagues developed a likelihood-ratio test to estimate the statistical significance of regions that show an apparent increase in the substitution rate on the human evolutionary branch (Siepel, et al. 2006). Siepel and cohort then applied this method to whole genome sequence data from humans, and several other vertebrates, to identify 202 regions that showed significant rates of human-specific evolution (Pollard, Salama, King et al. 2006), which they called human accelerated regions

(HARs). The most significant of these regions, HAR1, has 18 substitutions in 118 base pairs (relative to chimpanzees) and contains part of a novel RNA gene that is expressed in the human neocortex from seven to nineteen gestational weeks (Pollard, Salama, Lambert et al. 2006). Though the specific function of HAR1 is not known, it is tempting to speculate that it is related to the extreme growth in size and complexity of human brains in relation to other apes.

Pollard, Salama, King et al. (2006) found the substitutions at HARs show a weak-to-strong bias (i.e., tend to be from A or T to G or C), and that HARs tend to be in regions of high recombination. Both of these observations are consistent with the possibility that GC-biased gene conversion may play an important role in the creation of HARs (Galtier and Duret 2007; Katzman et al. 2010).

A complementary approach to identifying important regulatory changes involves analyses of gene expression levels using microarrays, or large-scale sequencing of RNA (RNA-seq) using next-generation sequencing (Romero et al. 2012). One intriguing hypothesis is that humans' unique cognitive abilities are due to changes in gene expression patterns in the brain during development (Caceres et al. 2003; Nowick et al. 2009; Xu et al. 2010), and there is some evidence in favor of this idea (Somel et al. 2009). More generally, measurements of gene expression within individuals of the same species, and between individuals of different species, are informative about the current or past action of natural selection for specific expression levels. For example, if between-species levels of gene expression variation are no larger than within-species levels, stabilizing selection on gene regulation is a likely explanation (Gilad et al. 2006). In contrast, if a higher expression level is observed specifically in one species, then directional selection for differential expression in that species is most likely operating. Recent studies have shown that the regulation of a majority of the genes in the genome evolve under evolutionary constraint, consistent with widespread stabilizing selection (Lemos et al. 2005; Rifkin et al. 2005). In addition, a substantial fraction of human and great ape genes show species-specific changes in gene expression levels that are best explained by recent positive selection (Gilad et al. 2006; Blekhman et al. 2008). Finally, it is important to note that gene expression levels are only an intermediate phenotype, and evidence of differential expression across species provides only a starting point for targeted studies to determine the genetic mechanism causing the difference and the function consequences (if any).

Gain or Loss of Genes

A related approach focuses on identifying and characterizing the gain or loss of genes in the human lineage subsequent to the divergence of humans and chimpanzees. Olson proposed that gene loss could be an important mechanism in the evolution of human-specific traits (Olson 1999). However, further studies have found that the rate of gene loss in the human-specific lineage is the same as the comparable rate in other great ape lineages (Kim et al. 2010; Prado-Martinez et al. 2013), suggesting that humans are not unusual in their rate of genic turnover. While this does not disprove Olson's hypothesis, it suggests that whatever role gene loss plays in species-specific traits is likely to be a general (rather than human-specific) phenomenon. In a few cases, more detailed studies have highlighted potential selective explanations for complete (Stedman et al. 2004) or partial (Xue et al. 2006) loss of genes in humans. Conversely, while several human-specific genes have been identified (Knowles and McLysaght 2009; Wu et al. 2011), most of these genes are of unknown function (but see [Buhl et al. 2006; Hu et al. 2012]), making their relevance to recent human evolution difficult to quantify.

Structural Changes

Humans have a diploid chromosome number of $2n = 46$, while the great apes have $2n = 48$ chromosomes (Yunis and Prakash 1982). Evolutionary genetic studies of the human chromosome 2 have highlighted additional evidence that this chromosome was formed by a fusion of two autosomes within in the past several million years (Dreszer et al. 2007; Auton et al. 2012; Ventura et al. 2012). Additional human-specific inversions (Yunis and Prakash 1982) and copy number variations (Dumas et al. 2007) were identified by conventional banding techniques, while more recent array-based comparative genomic hybridization experiments (Linardopoulou et al. 2005; Goidts et al. 2006; Wilson et al. 2006) and next-generation sequencing studies (Alkan et al. 2009) have identified many more large rearrangements and segmental duplications that are unique to the human lineage. When all forms of variability are taken into account, the estimated divergence between humans and chimpanzees increases from 1.2% (single nucleotide polymorphisms at aligned orthologous sites) to ~5% (Britten 2002). It is unclear what, if any, functional relevance many of these structural changes have in humans, though it may be relevant that regions near cytogenetically visible changes in the human genome are enriched for recent gene duplications and new genes (Fortna et al. 2004; Dumas et al. 2007).

Comparative Demography

The amount of divergence between two DNA sequences is, on average, directly proportional to the time since they last shared a common ancestor. By comparing patterns of genetic variation across multiple individuals from different populations, it is possible to make inferences about a species' demographic history including population migration, changes in population size, geographic structure, and admixture between diverged populations. By inferring demographic parameters in both humans and great apes, it can be determined if particular observations that are found in one species are common or unusual. This, in turn, allows for a more realistic assessment of the ways in which the human species might be unique.

Population Size

The current census size for the human population tops out at more than 7 billion individuals and continues to grow very rapidly. However, it is known that even as recently as several centuries ago, the human population size was orders of magnitude smaller. In fact, genetic studies have consistently found that two randomly chosen human chromosomes tend to differ from each other at roughly 1 in a 1000 base pairs, which is consistent with a long-term effective population size (N_e) of 10,000–15,000 (Li and Sadler 1991; Harding et al. 1997; Frisse et al. 2001). Here, N_e refers to the size of a randomly mating population that is expected to have the same levels of genetic diversity as what is observed. Although there are many reasons why N_e might be less than the census population size (Caballero 1994), the difference in magnitude is still immense, and requires explanation. The current belief is that for much of human history, the population sizes were much smaller, and it is only very recently (i.e., within the past 20-30 thousand years) that the population sizes have increased rapidly (Pluzhnikov et al.2002; Voight et al. 2005; Gutenkunst et al. 2009). Recent studies have identified an excess of very rare single nucleotide variants (minor allele frequency<0.1 %), consistent with explosive population growth over the past several thousand years, starting subsequent to the development and spread of agriculture (Coventry et al. 2010; Nelson et al. 2012).

In contrast, extant great apes are found exclusively in Old World tropical rain forests, and their ranges (and estimated census population sizes) have decreased dramatically over the past 200 years (Junker et al. 2012). While initial estimates of great ape genetic diversity from microsatellites were low (Wise et al. 1997; Cooper et al. 1998), subsequent studies of nuclear sequence variation have found that all great ape species, except for bonobos, have levels of genetic variation substantially higher than the levels of human genetic variation (Kaessmann et al. 2001; Fischer et al. 2006; Locke et al. 2011; Prado-Martinez et al. 2013). Since the underlying mutation rates are unlikely to be different between humans and great apes, the differences can be attributed to chimpanzees, gorillas, and orangutans having larger long-term N_e's than humans have. This finding highlights the value of a comparative demographic approach, as it emphasizes that the current human dominance (both in range and population size) is very recent—even though humans' ancestors had populated Eurasia and Africa for almost 2 million years, while the great apes have been confined to a much smaller area during that time. Most likely, there were more chimpanzees, gorillas, and orangutans around at any time prior to 50,000 years ago than there were humans.

Studies that estimate ancestral (effective) population sizes (N_a) provide additional evidence that humans' current N_e is unusually low. Takahata (1993) examined genetic diversity in the human major histocompatibility complex (MHC), and concluded that the diversity was consistent with a N_a of ~ 100,000. Other approaches, such as using the variance in human-chimpanzee divergence across the genome, the discordance of gene trees across the genome, or maximum-likelihood techniques, have estimated $N_a \geq 50,000$ for the population ancestral to humans and chimpanzees (Takahata and Satta 1997; Chen and Li 2001; O'hUigin et al. 2002; Wall 2003; Burgess and Yang 2008). While estimates of N_a can be inflated due to past population structure, the basic picture appears to be that almost all extant and ancestral ape populations have (or had) substantially more genetic variation (and larger effective population sizes) than extant modern humans.

Population Structure

An additional way of viewing the low N_e in humans is the idea that all extant people are genetically similar when compared with the great apes. Another facet of this idea is that all great apes consist of groups of diverged populations that are taxonomically considered to be separate species or subspecies (Groves 2006). Currently, there are the chimpanzee and bonobo (*P. troglodytes* and *P. paniscus* respectively), two gorilla species (*Gorilla gorilla* and *Gorilla beringei*), and two orangutan species (*Pongo pygmaeus* and *Pongo abelii*), and additional subspecies from each group, compared with just a single extant species and subspecies of *Homo sapiens sapiens*. Sister great ape species within the same genus can interbreed and produce fertile offspring in zoos, but not in the wild where their ranges generally do not overlap. The taxonomic differences between great ape populations are not purely semantic though, in that the genetic distance between great ape species is substantially larger than the genetic distance between isolated human groups (Fischer et al. 2006; Wall et al. 2008). Broadly speaking, the existence of multiple diverged populations that can admix and interbreed is the general pattern in catarrhine primates, including gibbons, macaques, baboons, vervets, and guenons (Jolly 2001; Arnold and Meyer 2006), with humans and a few isolated species (e.g., the siamang) as outliers. It is unclear why this is so, but perhaps some aspect of life-history behavior, mate choice, or migration facilitates the isolation (and genetic divergence) of nearby populations. Interestingly, just 50,000 years ago, the human species coexisted with at least three other archaic human groups, including Neanderthals, Denisovans, and *Homo floresiensis* (Wall and Slatkin 2012), and potentially several other diverged populations (Harvati et al. 2011; Curnoe et al. 2012). *H. floresiensis* coexisted with modern humans in island Southeast Asia as recently as 12,000 years ago (Morwood et al. 2005). Perhaps not coincidentally, these archaic human groups all disappeared around the same time as modern human populations started to increase rapidly in size.

X Versus Autosome Comparisons

Comparative studies of humans and great apes can also shed light on sex-specific differences, and life-history traits in each species. In a randomly mating population with equal

numbers of males and females, there are three X chromosomes for every four autosomes, leading to a 3:4 ratio in expected levels of diversity in X versus autosome comparisons. If a species is generally polygynous, there will be more breeding females than breeding males, which tends to increase the ratio of X-to-autosome diversity (Caballero 1994). Gorillas, who are strongly polygynous, are expected to have increased relative levels of X-linked diversity when compared with humans (weakly polygynous) and gibbons (monogamous). Concurrently recent positive selection, which decreases levels of genetic variation, is expected to affect the X chromosome more than the autosomes due to hemizygosity in males and the recessivity of some advantageous alleles. Analyses of human polymorphism data show the effects of both of these evolutionary processes (Hammer et al. 2008; Hammer et al. 2010; Keinan et al. 2009). Overall, the ratio of X-to-autosome diversity is much less than 0.75, which is consistent with the stronger effect of selection on the X chromosome. However, if the analysis is confined to regions far away from genes, where natural selection plays less of a role, the situation is reversed, with X-to-autosome ratios significantly higher than 0.75. A full analysis of whole genome sequencing data from the Great Ape Genomes Project (Prado-Martinez et al. 2013) is currently in process, and the results will be informative about the relative roles of natural selection, mating system, and sex-specific migration in shaping genome-wide patterns of genetic variation.

Comparative Population Genetics

As hinted at above, between-species comparisons can also be informative about other population genetic processes such as natural selection, mutation, and recombination. Two examples are discussed in greater detail below.

Recombination rates vary dramatically between individuals and between different regions of the genome. In particular, it is now well established that most recombination events occur in narrow 1–2 kilobase (kb) wide "hot spots", with almost two-thirds of all crossovers occurring in 10% of the human genome (Myers et al. 2005). Roughly 40% of these recombination hot spots contain a (partially degenerate) thirteen base pair sequence motif, which matches the predicted binding site of the PRDM9 gene, and is thought to be involved in double strand break formation (Baudat et al. 2010; Myers et al. 2010). PRDM9 evolves rapidly in metazoans (Oliver et al. 2009), and specific single nucleotide variants have been shown to strongly affect male recombination rates (Berg et al. 2010).

Recent studies of recombination in chimpanzees have shown that humans and chimpanzees generally do not share recombination hot spots (Wall et al. 2003; Ptak et al. 2004; Winckler et al. 2005; Auton et al. 2012), but most hot spots are shared across different human populations. Further, there is not a simple sequence motif that appears to be associated with the location of chimpanzee hot spots (Auton et al. 2012). This situation is not surprising, since there is a single

dominant PRDM9 allele at high frequency in humans (corresponding to the thirteen base pair [bp] sequence motif found near human recombination hot spots) but many low frequency PRDM9 alleles in chimpanzees. Even if PRDM9 plays a primary role in hot spot localization, it appears that the allelic diversity at PRDM9 in chimpanzees promotes a wide array of different hot spot locations in different chimpanzee individuals. Since large-scale detection of recombination hot spots is based on patterns of linkage disequilibrium, which reflect long-term average rates of recombination, it is unlikely that a particular sequence motif will be associated with hot spots unless there is a dominant (i.e., high-frequency) PRDM9 allele. It remains to be seen how common hot spot motifs are, but ongoing studies of recombination rates in all great ape species will provide a partial answer to this question (L Stevison and J Wall, unpublished data).

Whole genome sequence polymorphism data in great apes also help facilitate the search for polymorphisms that are shared by descent between multiple species. Theory suggests that such ancient shared polymorphisms are unlikely to arise by chance (Leffler et al. 2013), and are more likely due to long-lived balancing or frequency-dependent selection (e.g., selection for rare alleles, or selection for heterozygotes). One well-known example of ancient balancing selection is from the MHC, which has a primary role in the active immune system (Klein et al. 1993). Mutations in the MHC have been shown to be present before the split of humans from the great apes, and to persist as polymorphisms in multiple species due to selection favoring heterozygous genotypes for over 12 million years (Ayala 1995). Beyond this one well-known example, the evidence for ancient balancing selection is rare, in part because of the difficulty in distinguishing mutations that are identical by descent (i.e., arose before the split of humans and chimpanzees) from those that are identical by state (i.e., parallel mutations that happened at the same nucleotide site in multiple species). Whole genome sequence data makes it possible to distinguish between the two by looking for multi-SNP haplotypes shared across species (Leffler et al. 2013). Leffler and colleagues utilized complete genome sequences from fifty-nine humans and ten chimpanzees to identify 125 regions with haplotypes shared between humans and chimpanzees. These regions are significantly enriched for membrane glycoproteins, suggesting that genes involved in host-pathogen interactions are more likely to have been subject to ancient balancing selection. This idea is in keeping with previous studies of ancient balancing selection in humans (Klein et al. 1993; Segurel et al. 2012) as well as more recent balancing selection in humans and other species (Stahl et al. 1999; Hedrick 2011).

Great Apes as Reservoirs of Disease

One area where great ape genomics is of direct relevance to human health involves infectious diseases that are shared across species (i.e., zoonosis). The most well known example concerns HIV-1, a strain of human immunodeficiency

virus that is pandemic in humans (Sharp and Hahn 2011). Initial genetic studies of HIV found that the disease was closely related to other lentiviruses found in African apes and monkeys. It has been shown that HIV-1 is similar to SIVcpz, a simian immunodeficiency virus found in the central chimpanzee *Pan troglodytes troglodytes* (Huet et al. 1990). Subsequent studies of natural chimpanzee populations confirmed *P. t. troglodytes* as a natural reservoir of HIV-1, and indicated that there had been multiple transmission events of HIV from chimpanzees to humans (Keele et al. 2006). Chimpanzees in turn are thought to have acquired SIVcpz relatively recently from eating infected monkeys (mangabeys, guenons, or both). There is some evidence that chimpanzees infected with SIVcpz can develop AIDS (Sharp and Hahn 2011), but there is a possibility that studies of how chimpanzees (and gorillas who are infected by SIVgor) physiologically respond to SIV may provide some insight into how humans can treat current HIV-1 infections.

Conservation Biology

One of the primary motivations for studying great ape demography is to help inform advocacy and policy decisions for promoting the conservation, health, and genetic diversity of our evolutionary cousins. All great ape species are considered to be Endangered or Critically Endangered by the International Union for Conservation of Nature (IUCN 2012) due to the recent drastic reduction of their rainforest habitat (Junker et al. 2012). From a conservation perspective, the priority is obviously to increase (or maintain) suitable habitats for great apes, and to eliminate (or reduce) human-mediated mortality, but there is an important role for genomics in helping conservation biologists focus their efforts. DNA-based studies can help identify populations that are genetically distinct from all others, which can elevate the importance of preserving them as a previously unknown reservoir of genetic diversity. For example, a study of orangutan mtDNA helped the recognition of the Sumatran orangutan as a separate species (Xu and Arnason 1996), and a study of autosomal SNP variation argued for the creation of a fourth chimpanzee subspecies, *Pan troglodytes ellioti* (Bowden et al. 2012). Genetic studies have also estimated the extent of recent population decline in orangutans (Goossens et al. 2006) and chimpanzees (Campbell et al. 2008), and identified important evidence for long-range migration in the Sumatran orangutan (Nater et al. 2013). Finally, additional analyses are possible with widespread whole-genome sequence data in great apes. To some extent, the provenance of captive animals can be inferred from large-scale genetic data, and recent work suggests that most captive individuals are genetically admixed from two, or more, distinct wild-born populations (Prado-Martinez et al. 2013). Prado-Martinez and colleagues also utilized runs of homozygosity (McQuillan et al. 2008) to quantify the extent of inbreeding in different great ape species. Bonobos had large homozygous tracts similar to isolated human groups that are known

to have small population sizes (e.g., the Karitiana from Brazil), suggesting that inbreeding is an ongoing concern in extant bonobo populations.

Conclusions

Given the dire situation that all great ape populations currently face, there is added motivation for researchers to learn as much as possible from their genomes, both to provide additional justification for conservation efforts and because such studies may be impossible in the not-too-distant future. As highlighted above, great ape genomic studies have already been highly informative in regards to human biology, human history, and the effects of natural selection. The great apes are likely to remain of critical importance for future human genetic studies, even without the benefits of manipulative studies that are used in model organisms such as the macaque or the mouse.

Acknowledgments

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