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TITLE: The diversity of primates: from biomedicine to conservation genomics

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Primate Diversity and Genomics

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ABSTRACT (150 words max)

Until now, the field of primate genomics has focused on two major themes: understanding human evolution and advancing biomedical research. We propose that it is now time for a third theme to receive attention: conservation genomics. As a result of anthropogenic effects, the majority of primate species have become threatened with extinction. A more robust primate conservation genomics will allow for genetically informed population management. Thanks to a steady decline in the cost of sequencing, it has now become feasible to sequence whole primate genomes at the population level. Furthermore, technological advances in non-invasive genomic methods have made it possible to acquire genome scale data from non-invasive biomaterials. Here, we review recent advances in the analysis of primate diversity, with a focus on genomic datasets across the radiation.

INTRODUCTION: The three themes of primate genomics

The field of non-human primate (NHP) genomics began 15 years ago with the release of the initial sequence assembly of the chimpanzee genome(1). As our closest extant evolutionary relative, it was hoped that this species offered the potential to expand our understanding of the genetic underpinnings of many characteristics that distinguish us from other primates. Among the objectives of sequencing the chimpanzee's genome was to catalogue the molecular differences with humans, and therefore offer a potential avenue to interrogate the genetics underlying human specific traits such as large brains and the associated higher cognitive capacity, habitual bipedalism, or the ability to produce and understand speech(2). The availability of a genome sequence for a close evolutionary relative has proven invaluable to our understanding of the human condition, both from biological and cultural perspectives (e.g. Kitzmiller v. Dover). Its initial comparative analysis showed marked differences in genes relating to inflammatory response, apoptotic mediators, parasite resistance, and sialic acid metabolism, among other traits. Our curiosity to better understand the evolutionary trajectory of our own species was among the main driving forces to fund such studies, and understanding human evolution remains a major theme of NHP genomic research(1, 3).

Beyond the chimpanzee, genomic resources for all ape genera followed in a first wave of NHP genomes. The initial assemblies for the orangutan(4), gorilla(5) and bonobo(6) and gibbon(7) reference genomes helped clarify our understanding of the evolutionary relationship of these species and humans on the molecular level. This includes marked differences in mobile element insertion rate and structural genomic rearrangements(4), significant proportions of incomplete lineage sorting between human-chimpanzee-gorilla(5), as well as human-

chimpanzee-bonobo(6), and a clear molecular phylogeny of the relationship between extend great apes(5), including humans. These initial comparisons were mainly based on single base differences in protein coding regions, as well as small insertions and deletions, mainly because of the limited resolution and quality that early whole genome shotgun assemblies provided. However, given that the human and chimpanzee genomes are on average 99% identical, and a small portion of it comprises protein coding regions, few examples of simple protein coding human specific innovations have been found. Nevertheless, several important human innovations seem to lay in regions of accelerated evolution and rapid structural change such as segmental duplications(8), a particularly important source of variation in the African great ape lineage(9, 10). For example, human accelerated regions (HARs), i.e. small regions that are conserved throughout other evolutionary branches but underwent accelerated evolution in humans, have been shown to be important regulators of genes involved in neural development, cognition, and social behavior, and their disruption has been associated with symptoms of autism spectrum disorders(11, 12). Another example is NPAS3, a neural transcription factor that is regulated by enhancers highly enriched in HARs, whose disruption has been associated with schizophrenia(13). Furthermore, several different genes within human specific segmental duplications such as SRGAP2, ARHGAP11B, and TBC1D3 are involved in the development of the neocortex and its complex folding(14–17). Analogous to HARs, human conserved deletions are regions that are conserved throughout other branches, but have been deleted specifically in the human lineage. Examples include the loss of a forebrain subventricular zone enhancer that regulates GADD45G, a gene associated with repressed cell proliferation whose down regulation might therefore be responsible for the enlarged human neocortex(18). Another example is the loss of an enhancer that regulates an androgen receptor responsible for the development of penile

spines, which have been lost specifically in the human lineage(18). The above examples not only highlight the fundamental importance of generating NHP genome assemblies, which are crucially driving these discoveries and our understanding of human biology(18, 19). They also underline the necessity of having accurate, high quality reference assemblies available to perform comparative analysis of structurally challenging regions of the genome, several of which underlies some of the key features that make us unique (19, 20).

The second major motivation to develop NHP reference assemblies has been to characterize the genomics of biomedically relevant model species. This approach is based on the assumption that the genetics underlying clinically relevant traits in NHPs would be useful for translational research into human health amelioration(21). Given the evolutionary proximity and phenotypically similarity between humans and NHPs, several species had been widely used for decades as human disease proxies, albeit without explicit reference to their genetics. This is particularly true for studies relating to neurobiology. The most extensively characterized species in this context is the rhesus macaque, whose impact on biomedical research was immortalized in 1937 by lending its name to the blood rhesus factor(22). Rhesus and cynomolgus macaques, have been a focus of biomedical research on infectious diseases such as Influenza and HIV/AIDS, cardiovascular diseases, diabetes, and other maladies; their importance as such led to the early generation of reference assemblies for both species(23, 24)**.** Other examples of biomedically relevant NHPs include species of baboons(25), vervet monkeys(26), and common marmosets(27), the latter of which have become an important neurobiological model species. It is also important to recognize that many NHPs inhabit wide geographic ranges and have high degrees of intraspecific variation. For example, rhesus macaques from China and India are known to show different disease progressions and viral load upon infection with SIV(28).

Perhaps the most impactful emerging biomedical possibility is the directed genetic engineering of primate models. While transgenic primate models have been around for some time, systems such as CRISPR-Cas9 offer a new approach that uniquely benefits from detailed knowledge of genome architecture to genetically engineer animal models at specific targets(29). Finally, it should also be noted that an ancillary benefit of the aforementioned genomes being generated for biomedical purposes was their invaluable contribution to comparative and evolutionary genomics. The rhesus macaque and common marmoset assemblies allowed for the first glances at the genomics of monkeys (23, 27). They also served as critical outgroups to the great apes, enabling the detection of lineage specific differences between humans and chimpanzees.

Expanding our understanding of human evolution and conducting biomedical research are both legitimate foci of attention for primate genomics; however, we propose that an emerging third theme merits attention at an accelerated pace: conservation genomics. Currently, around 60% of the over 500 described primate species are threatened with extinction, 75% have declining population sizes, and several are expected to vanish in the very near future(30). This enduring extinction crisis is caused by anthropogenic factors, and the study of genomes from several primate species has already revealed reductions in genetic diversity, both in historical and recent times, some of which likely represent recent human impacts (31–36). The study of evolutionary processes and the genomics of different primate populations has the potential to beneficially impact conservation by providing information on the "genetic health" of a species, population, or individual. Furthermore, it might allow for directed actions that assess extinction risk by identifying the potential of a species to adapt to ongoing environmental changes. It is becoming increasingly clear that genetically informed conservation management could mitigate the loss of biodiversity(37, 38). This is not only the case on a population level, by estimating

parameters such as genetic diversity, effective population size or inbreeding, but also at the individual level by upon performing interventions such as genetic rescue. Correctly understanding the genetic makeup of species and individuals can be crucial for the management, particularly for species with small effective population sizes, as uninformed conservation actions, even when taken with the best of intentions, can have perilous outcomes(37).

As the global loss of biodiversity proceeds at an accelerating rate, conservation efforts are more critical than ever. It is often claimed that the high cost of genomic analysis renders conservation genomics an unjustifiable alternative to traditional "boots on the ground" approaches. However, a recent, dramatic decline in sequencing costs, coupled with advances in noninvasive molecular techniques facilitating whole genomic analysis, have changed the dynamic of this situation. We are at the beginning of an era of cost-effective conservation genomics, and have the opportunity to help mitigate the worst outcomes of the coming extinction crisis. The comprehensive study of base levels of diversity and its determinants across the primate radiation is not only timely and important, but for the first time realistic. We have structured this review to provide the reader with a primer on the current and future state of primate conservation genomics, as follows: 1) Primate diversity and biogeography, 2) Primate conservation; 3) The current state of knowledge in primate genomics; 4) The major limitations and challenges of primate genomics; 5) Methodological advances for non-invasive genomics; 6) The future of primate genomics.

PRIMATE DIVERSITY AND BIOGEOGRAPHY

Primates are members of the Euarchonta grandorder, which also includes tree shrews, and colugos. Molecular evidence places colugos as the sister taxon to primates(39, 40), likely

splitting during the late Cretaceous (~ 86 Ma(40)). Adaptive explanations for euprimate (primates of modern aspect) origins began with "the arboreal theory" of Smith(41)and Jones(42). They proposed that a terrestrial euprimate ancestor with generalized morphology (i.e. lacking the specializations of the primate body plan) transitioned to arboreality, undergoing selection for morphological characteristics that facilitated life in this new niche. Most modern explanations for euprimates origins (43–47) derive from the arboreal theory, but focus on adaptation to a fine (terminal) branch niche. It has been proposed that terminal branch life, along with a dietary shift toward predation on insects at night(44), a relaxation of terrestrial selective pressures (45), and coevolution with angiosperms and consumption of newly available foods(43) enforced a gradient selecting for the evolution of the primate morphotype, which features grasping prehensility and stereoscopic vision.

Extant primates are distributed across 90 countries in South and Central America, Africa, and Asia, with two thirds of species located in tropical regions of Brazil, Indonesia, Madagascar, and The Democratic Republic of Congo(30) (Figure 1). To a large extent, primate species diversity is associated with latitude and rainfall patterns, both of which influence availability of tropical forest habitat and abundance of food resources(48, 49). The geographic breadth of a primate species often results from local niche effects, such as the degree of ecological specialization in dietary breadth and habitat use(48, 49). The global distribution of primates has been influenced heavily by historical biogeographic effects, such as vicariance, dispersal, and refugia. For instance, the overwater dispersals of primates from Africa into the Americas(50–52) and Madagascar(53, 54) allowed for rapid adaptive radiation into previously unfilled niche space. Presently, 504 species of primates have been classified into 79 genera, and 16 families(30) (Figure 2). At the broadest level, primates comprise two semiorders: Strepsirrhini and

Haplorhini. Nominally, this distinction refers to the presence of a wet nose with a split lip versus a dry nose with an intact lip, respectively, although other morphological characteristics (e.g. postorbital bar/closure, presence of a tapetum lucidum, vomeronasal organ, and relative brain size) coincide with this division, which is strongly supported by molecular evidence(55). For the sake of consistency with the literature, we follow the widely-cited taxonomic framework of Estrada *et al*.(30), which relies on classification by the International Union for Conservation of Nature (IUCN). We acknowledge that the number of primate species changes rapidly, and some primatologists propose deviations from these numbers.

Strepsirrhini

The 137 Strepsirrhini species are composed of two infraorders: lemuriformes and lorisiformes, accounting for 7 of 16 primate families. The origin of strepsirrhines remains a subject of debate, but they are often considered to be descendants of or a sister taxa to the Eocene adapiform primates(56). The lemuriformes (colloquially "lemurs") are endemic to Madagascar. After splitting from the lorisiformes as early 65 Ma(57) in mainland Africa and dispersing across the Mozambique channel(53, 54), ancestral lemurs encountered an ecosystem that was not only relatively free of competitors and predators, but also profoundly environmentally heterogeneous, which led to a remarkable adaptive radiation of 103 extant species and 5 families (cheirogaleidae, dwarf and mouse lemurs; daubentoniidae, aye-ayes; lemuridae, "true" lemurs; lepilemuridae, sportives; and indriidae, indri, wooly lemurs, and sifakas)(58). Extant lemurs range widely in size from diminutive mouse lemurs (*Microcebus berthae*) to the medium-bodied indri (*Indri indri*), and display a wide range of activity patterns, lomotor specializations, diets, and social structures. Many lemurs are distinguished from other

primates by peculiar phenotypes such as a dental tooth comb, vertical-clinging and leaping locomotion, torpor, female dominance, and nocturnality(55, 59). However, prior to the arrival of humans on Madagascar ~2 Ka, the radiation of Malagasy primates was even broader, when several groups of now extinct subfossil lemurs occupied a wider niche space(60). Many of these subfossil taxa were larger (e.g. 200 kg *Archaeoindris*), diurnal, and slower (e.g. "sloth lemurs" such as *Paleopropithecus*), rendering them easier hunting targets(55, 60). The lorisiformes, while more broadly distributed than the lemuriformes, are a substantially less diverse radiation (29 species and 2 families) inhabiting Africa and Asia. They are generally characterized as nocturnal, small-bodied, arboreal, solitary foragers; however, the two families diverge ecologically. The lorisidae (lorises, pottos, and agwantibos) have low metabolic and developmental rates and a cautious, slow moving locomotion, whereas the galagidae (galagos/bushbabies) are highly agile leapers with a faster life history(61, 62).

Haplorhini

367 species and 8 families of Haplorhini are classified into three main groups: tarsiiformes, platyrrhini, and catarrhini (the latter of two of which can be lumped together as anthropoidea). The haplorhini are widely distributed across the globe, occupying all primate habitat countries, with the exception of Madagascar. The great majority of haplorhini are anthropoid primates (monkeys and apes), which are subdivided into two infraorders: platyrrhini (monkeys in the Americas), and catarrhini (monkeys and apes in Africa and Asia). Anthropoids (monkeys and apes) can be distinguished by numerous anatomical features, most notably a fused mandible, postorbital closure, nails on all digits, absence of the stapedial artery, and large brains(55). The extant tarsiiformes (tarsiers) are a single lineage with 11 species that until

recently, was classified as a one genus, *Tarsius*. Tarsiers are endemic to the islands of Sundaland, predominantly Greater Mindanao (*Carlito*), Sumatra and Borneo (*Cephalopachus*), and Sulawesi (*Tarsius*)(63). Phenotypically, tarsiers present a mosaic of traits common to strepsirrhini and anthropoidea, and resemble the Eocene Omomyidae(55). Tarsiers are small bodied, nocturnal, faunivores, characterized by extreme morphological adaptations to arboreal leaping and enormous eyes (each larger than their brains)(63, 64). This phenotypic mosaicism is of particular interest, given that tarsiers diverged from anthropoids 58 Ma, shortly after the strepsirrhine/haplorrhine split(65).

The platyrrhines are composed of 171 species in 5 families of monkeys (callitrichidae, marmosets and tamarins; cebidae, capuchin and squirrel monkeys; aotidae, owl monkeys; pitheciidae, titis, sakis and uakaris; and atelidae, spiders, howlers, woolies, and muriquis). Extant platyrrhines occupy a wide range of habitats (tropical rainforest, subtropical rainforests, tropical dry forest, and savannah) from southern Mexico through northern Argentina, but are most widely distributed throughout Amazonia(66). Platyrrhines are remarkably speciose, but in some respects ecologically limited in comparison to strepsirrhines and catarrhines. Platyrrhines have small to medium body sizes, and are almost exclusively diurnal arboreal quadrupeds(55). However, platyrrhines do display a range of dietary regimes and social/mating systems, and in some cases have uniquely or independently evolved traits including prehensile tails (cebidae and atelidae)(67), secondarily evolved claw-like nails (callitrichidae)(68), nocturnality (owl monkeys)(69), routine trichromatic color vision (howlers)(70), and tool use (cebidae)(71). The lineages and origins of platyrrhines have been notoriously difficult to explain, although the morphological affinity between Eocene/Oligocene platyrrhines and contemporaneous north African anthropoids, supports the hypothesis that the first platyrrhines rafted to South America in

a trans-Atlantic vicariance event and radiated rapidly(50–52). Several fossil and subfossil platyrrhines dating to the Miocene through Holocene have also been found in the Caribbean, from species likely to have been extirpated by humans(72).

Extant catarrhines include 185 species in 3 families of monkeys and apes from Africa and Asia. Compared to other primates, catarrhini tend to have larger body masses, brain sizes, extended life histories, more terrestrial locomotion, greater evidence of sexual selection, and routine trichromatic vision(55, 73). The vast majority of catarrhini are monkeys of the family cercopithecidae (160 species), which is composed of two distinct subfamilies: the cercopithecinae (baboons, geladas, kipunji, macaques, guenons, vervets, mangabeys, mandrills, etc.) and colobinae (colobus monkeys, langurs, and odd-nosed monkeys). The cercopithecidae have the broadest geographic range of any non-human primate--macaques alone ranging from North Africa to India, Sundaland, and Japan--and are increasingly found at the interface with human settlements(55, 74). Some also occupy geographic and climatic extremes, such as the Yunnan snub-nosed monkey, which has adapted to high-altitude and low temperatures at 4,500 m in the Tibetan plateau(75, 76). The cercopithecidae often have complex, hierarchical social systems, which are particularly well-studied in the baboons(77). Guenons often form multispecies groups and display a remarkable variety of coloration and facial patterning, likely signaling for species discrimination(78). The colobinae have adapted to a highly folivorous diet, evolving a sacculated stomach allowing for foregut fermentation of cellulose(32). The hominoidea (apes) comprise 25 species in 3 families. The apes are substantially less speciose than the monkeys, although, a wide array of apes lived during the Miocene, predominantly in Europe and Africa(55, 79). Extant apes are somewhat biogeographically restricted, only being found in southeast Asia and sub-Saharan Africa. The unifying trait of apes is the lack of a tail,

however, they typically have more orthograde body postures, large brains, and slow life histories(55, 80–82). The hylobatidae (small apes, or gibbons) are the substantially more species rich family (19 species), but are restricted to southeast Asia. Gibbons are dedicated arborealists that have adapted morphologically to a distinct form of arm-swing suspensory locomotion (brachiation)(83). They sing complex vocal duets and while long mischaracterized as monogamous, substantial social/mating system diversity exists across gibbon species(84). The hominidae (great apes) include bonobos (gracile chimpanzees), common (robust) chimpanzees, humans, gorillas, and orangutans. Relative to other primates, great apes have been extraordinarily well studied; they have complex social systems, long lives, high intelligence, the capacity for tools use, and large body masses.(73, 85–87). Given their morphological and geographic range, identifying the lineages leading to gibbons, great apes, and humans in African and Asia remains a subject of debate(79, 81).

PRIMATE CONSERVATION

As it stands today, the world's primates are in peril(88). Despite the widespread distribution of primates, human activities will likely cause the extinction of most species if present trends continue unabated. The IUCN quantifies extinction risk using species data on population decline, population size, range area, and quantitative population viability analysis(89). Ordinal IUCN extinction risk levels range from least concern to critically endangered. Of 504 primate species from which data could be assembled reliably by the IUCN in 2017, about 60% are threatened with extinction; broken down by major biogeographic areas, this accounts for 87% of primates in Madagascar, 73% in Asia, 37% in mainland Africa, and 36% in the Americas(30) (Figure 1). Members of all 16 primate families are threatened, and for 10

families at least half of species are threatened(30). The risk is of particular concern for the lemuroidea and hominoidea, and to a lesser extent the cercopithecidae and tarsiidae. While many of the platyrrhini and lorisoidea remain at high risk, the threat is less immediate at the family level. The overarching threats to primates are anthropogenic habitat loss (primarily deforestation and fragmentation resulting from agriculture, logging, and livestock), hunting pressure for the bushmeat trade, and to a lesser degree mining, civil unrest, capture for medicinal uses, and climate change(30, 90, 91). For any given species, the immediate causes of these risk levels vary in accordance with local pressures, as well as innate biological traits such as life history, body mass, and trophic level(92). Nonetheless, the root concern remains human population growth and development, often facilitated by the expansion of roads into previously inaccessible areas(90). Addressing the realities of primate conservation in the 21st century remains an ongoing challenge. Isolating large stretches of forest from human activity (fortress conservation) is a colonial perspective that often conflicts with the basic human rights of indigenous peoples(93, 94). Efforts that embrace ethnoprimatological perspectives(95, 96) by partnering with people who occupy and surround primate habitat are vital to future conservation management.

It is also important to acknowledge the role that species delimitation plays in conservation assessment and management, as the number of taxonomic groups has increased sharply in recent years (38). This increasing species richness is not primarily the result of previously unknown primates being discovered in unsurveyed forests. Rather, the trend toward taxonomic splitting stems from improving molecular data that allow for phylogenetic discrimination among cryptic taxa, and conservation pressures to classify threatened populations as distinct; whether each species is valid depends upon the species concept employed (38). Of particular use is the General Lineage Species Concept(97), which defines a species as a

metapopulation lineage that is separately evolving. Under this framework, the co-occurrence of species delimiting criteria (e.g. reproductive isolation, phenotypic cohesion, morphological distinction, reciprocal monophyly, etc.) provide increasing confidence that lineages are separate species. Given the ambiguities of species as a taxonomic unit, some authors propose the use of conservation or evolutionarily significant units(98, 99), which can allow for a more flexible degree of diagnostic differentiation for conservation management purposes. There remains ongoing debate as to what constitutes a unit of conservation(99), given the realities of cryptic speciation and variable degrees of genetic differentiation in populations. Analyzing whole genomes opens the possibility to assess the ancestry of given genomic segments, and thus to potentially make more informed decisions about which populations merit more focus.

PRIMATE POPULATION GENOMICS

Despite ever improving access to genomic methods, there are still comparatively few population genomic scale studies of primates. Several genomic datasets have been produced with a focus on human evolutionary genomics and biomedical research, but the vast majority of species remain unexamined. Given the dire circumstances facing many primates, a broad expansion of population genomics across the order focusing on underrepresented taxa could have profound conservation implications. As an example, WGS data can be used to reconstruct the demographic history of a species by assessing fluctuations of effective population sizes over time via coalescence based methods (100–102). Such an approach has the potential to determine whether the reduced genetic diversity observed in a given species is the result of an historical bottleneck, and to assess the impact of drift on future viability. Furthermore, it can be used to measure the extent of runs of homozygosity and their overall track length, which provide insight

on the amount and timing of inbreeding within a species (103). WGS also allows for the assessment of the functional significance and impact of genetic variation, such as putatively deleterious alleles, and their frequency within a population or species (33). Together, these measurements allow us to take a snapshot of the "genomic health" of a species, and inform potential further actions. Here, we review the whole genome sequencing literature across the primate radiation and highlight potential implications for conservation.

Apes

Among the first group of primate species to be studied at the whole genome level were the great apes. In the last decade, whole genome analysis has revealed a 3-fold range of genetic diversity among great ape species, as well as ample support of inbreeding within wild populations of several species. Within the great ape lineage, non-African humans, western chimpanzees, bonobos and eastern lowland gorillas, were initially found to exhibit the lowest levels of genetic diversity, whereas Sumatran orangutans show the highest, despite a significant recent population collapse(31). Early analysis of the genomes of six great ape species (including humans) showed a detailed picture of their recent evolutionary history, revealing periods of past expansions and contractions of effective population sizes and evidence of gene-flow between different subspecies of common chimpanzees(31). Subsequent analysis of additional chimpanzee genomes demonstrated that ancient gene-flow was not limited to subspecies of common chimpanzees, but also occurred between common chimpanzees and bonobos (36), as well as from an extinct ghost lineage into bonobos(104). Genomic assessments of gorillas have also had substantial conservation implications, particularly for mountain gorillas, the iconic subspecies made famous through the work of Diane Fossey. Mountain gorillas are among the most

endangered great apes--although they have recovered to a census size of ~1000 individuals thanks to intensive conservation efforts(33, 105)--and have the lowest levels of genomic diversity among the great apes. They show evidence of long term population decline, with levels of genetic diversity reaching less than ⅓ of that in eastern lowland gorillas and most recent estimates of an effective population size sum to only ~270 individuals(33). Their genomes are covered in megabase-scale runs of homozygosity that amount to over ⅓ of the total length, evidencing long term inbreeding within their small population. Nevertheless, despite the diminished genetic diversity there does not seem to be an excess of deleterious variation within their genomes. Furthermore, detailed analyses of temporal changes in allelic diversity over the last 100 years have been performed using museum samples from both mountain and Grauer's gorillas(35). Grauer's gorillas have experienced a population decline of ~80% over the last 20 years, whereas mountain gorillas seem to have had more stable populations overall in that time period, albeit very small ones. Correspondingly, the temporal sequence of samples provided evidence for a significant decrease in allelic diversity with an associated increase in mutational load for the Grauer's gorilla. Contrary to the example of gorillas, recent genetic and morphometric analysis of orangutan genomes revealed high levels of diversity leading to the definition of a new species, the critically endangered Tapanuli orangutan, which was previously lumped together with Sumatran orangutans. This species has an estimated census size of only 800 individuals, the lowest of any great ape and thus immediately became a major focus for conservation efforts(34).

Gibbons are the most species rich family of apes, with four genera that encompass 19 currently recognized species. With the exception of the eastern hoolock gibbon all of them are categorized as endangered or critically endangered by the IUCN, some of which are among the

most threatened of all primates. For example, the Hainan gibbon has an estimated ~25 individuals left in the wild, making it the rarest known primate(106). Five species of gibbons have whole genome sequences available, and genetic diversity within them ranges roughly 2-fold from 0.0008 in the pileated gibbon to 0.002 in the northern white-cheeked gibbon. However, these are point estimates, based on at most 2 individuals per species(7, 107). The four gibbon genera underwent a nearly instantaneous radiation, with large amounts of incomplete lineage sorting and potential gene-flow, which makes it particularly challenging to determine their precise phylogenetic relationship, and no clear overall topology based on the nuclear genome has been established. Population scale-resequencing data might be able to address these issues, and thus may also help to delimit and define potential units of conservation in more pressing need of focused interventions within the somewhat blurred species delimitations of this family.

Cercopithecidae

The six species of baboons have complex phylogenetic relationships with lineages that formed through a series of divergence and introgression events(25, 108). The most dramatic example is the Kinda baboon, a species that was formed by the hybridization of chacma and hamadryas baboons, resulting in a genomic makeup in which both parental species contributed almost exactly half to its genome(25). Chacma baboons are furthermore currently the only NHP species for which an ancient genome exists. This provides a time estimate of genomic diversity for chacmas, showing no significant loss thereof over the last ~6000 years, as well as a stable population of high continuity within southern Africa(109).

Despite the importance of rhesus macaques for biomedical research and the fact they are among the most well studied NHP, few fine-grained analysis of genomic variation and

comparisons of individuals from different populations based on whole genome sequences exist, especially for wild individuals(110–112). The recent analysis of 133 genomes from captive colonies of predominantly Indian origin consolidated a divergence estimate of ~200k years ago between Indian and Chinese populations, with a subsequent bottleneck in the Indian population likely coinciding with its westwards expansion(111). Estimates of their genomic diversity overall are roughly twice as high as in humans, and Indian individuals show slightly lower levels than those of Chinese origin**.** Furthermore, the comparison of 81 whole genomes of wild-born Chinese rhesus macaques from four different subspecies showed marked population differentiation among them. There seem to be several local adaptations within the different subspecies that potentially affect biomedically relevant traits(111). Rhesus macaques have been found to harbor segregating variants that are putatively disease causing in humans(111, 112). These facts underline the importance of understanding the genomic makeup of individuals that are used in a biomedical context, as responses to specific experiments might differ between individuals from different populations, as well as between the model species and humans themselves. Rhesus macaques share a broad geographic distribution and adaptation to a wide range of ecological backgrounds with humans, and are among the only primates to do so. With large effective and census populations sizes, and low levels of deleterious variation they are currently of limited concern. However, the capture of wild animals for export to foreign research colonies at rates of ~50.000 individuals per year has led to severe population declines in India in the past(113). A similar situation might lead to a rapid extinction of a species, despite large population sizes(114). The crab eating macaque has also been the target of genomic analysis, much for the same reasons as the rhesus macaque, although to a lesser extent. Most genomic

variation data from this species focuses on a colony on Mauritius, and might therefore represent an underestimation of the diversity in the natural species range(24).

Vervet monkeys are an important natural host for SIV with specific adaptations to cope with its infection, and as such have emerged as a model species to study HIV. Currently, six species are recognized, which generally exhibit high genetic diversity, and have large effective populations sizes that have been comparatively stable over time(26, 115). The recent analysis of 163 whole genomes of 5 vervet species showed ample evidence of interbreeding between different members of the genus. Most vervets are of limited conservation concern, with only one species currently being classified as vulnerable. However, vervet genomic data have informed recent analysis of an endangered guenon sister taxon, the dryas monkey. The analysis of the dryas genome revealed bidirectional gene flow between itself and several vervet species in the past(116). It shows high genetic diversity and little genetic load, hinting at good chances of long-term survival of the species despite a low census size (~250 individuals), given adequate conservation measures. A mitochondrial phylogeny groups the dryas monkey together with the vervets, whereas a nuclear one clearly positions them as a sister taxa. This also underlines the importance of having genome sequences for species of little concern available, as they can be highly informative when trying to understand the demographic history and population dynamics of species of higher concern.

Snub-nosed monkeys are among the few colobines to have their genomes sequenced. Analysis of 4 species revealed serial bottlenecks resulting in very low levels of genetic diversity within present day populations. Some species are also characterized by large amounts of homozygosity, such as the Myanmar snub-nosed monkey, in which ~⅓. of the genome is

covered by runs of homozygosity (27). The more recent analysis of 9 langur species also showed low long term effective population sizes for several of them (117).

Platyrrhini

Although a comparatively low proportion of apes and cercopithecidae have been included in genomic analysis, their numbers are high relative to the remaining clades of primates. Platyrrhines for example, are the most species rich group of primates, yet they are severely underrepresented in genomic analysis. Currently, reference assemblies for 11 species exist (Kuderna et al., 2020 in press), yet there is little genomic information of wildborn populations available. The genome of the common marmoset has been sequenced and characterized, as this species is an emerging model for neurobiological research(27). While the study also assessed polymorphism data by resequencing 9 additional individuals, they are all derived from captive research colonies(27) The situation is similar for Owl monkeys(118). Recently, white-faced capuchin genomes from Costa Rica showed moderately low levels of genetic diversity and inbreeding, with small effective population sizes that have declined in the past(119).

Strepsirrhini

The most underrepresented clade in terms of genomic resources are the strepsirhines, and within them the lemurs of Madagascar. This island alone is home to roughly 20% of primate species, more than 90% of which are threatened with extinction(30). Some reference assemblies for lemurs have been generated, but as the radiation of the clade is much older than that of haplorhines, the strategy of using the assemblies of different species, which can be highly informative(31), is much more challenging to apply(120, 121). Levels of genetic diversity span a

broad range within the clade, and are lowest within the aye-aye, likely as an effect of its large home ranging size and low population densities(122, 123). Recent analysis of four dwarf lemur species unveiled recent population declines and partially high levels of inbreeding in some species, combined with ancient gene-flow events across them(124). Population declines have also been observed in greater bamboo lemurs(125). Lastly, several recently extinct lineages of lemurs have remains in the form of sub-fossils that are in theory within the technological time-range of ancient DNA studies. While there are not yet any successful efforts to generate whole genome sequences of these species, they could be informative on the demographic history of primates on the island, and the potential impact humans have had on them.

MAJOR LIMITATIONS OF PRIMATE GENOMICS

The primary limitation of primate genomics remains the inability to acquire a large number of high-quality samples from multiple individuals across broad geographic distributions. Blood and tissue samples can be readily obtained from captive breeding populations and medical facilities, and to a lesser extent, zoos and rehabilitation centers. However, this represents a vanishingly small proportion of primate species diversity and an exceptionally small number of individuals per species. Most zoos only house a subset of charismatic primates, and little verifiable information about the biogeographic origin and pedigree of the animals is often known(126). Collecting blood or tissue samples from free ranging primates is challenging. Trapping or darting primates is possible in some conditions(127), but is under increasing scrutiny as managers of protected reserves seek to avoid non-essential health and behavioral consequences to protected species. Tissue samples can be collected from bushmeat markets(128), sustainable partnerships with indigenous hunters(96), or opportunistically when

deceased individuals are discovered by field biologists, but these situations only arise extraordinary circumstances. Wherever possible, induced pluripotent stem cells should be generated from high-quality tissue samples for future conservation research (eg. San Diego Frozen Zoo and Barcelona Cryo-Zoo cryofacilities) (129).

As a consequence of these challenges, molecular primatology has prioritized non-invasive sampling, particularly of feces (130–132) and to a lesser extent hair(133) and urine(134). Collecting non-invasive samples is not without its own set of challenges. The primary determinant of success in non-invasive sampling is often whether or not a given primate group is habituated to human observers. When a population of primates has undergone long term study, individuals are less likely to scatter in human presence, and can often be identified by distinctive facial features. In such cases it can be possible to collect multiple fecal samples from a large number of individuals over multiple years(135). For species of particular interest, research consortia can pool resources to assemble near species-wide sampling, but such cases are truly exceptional and not representative for most primates. While an impressive number of primates species have undergone field observation, almost all free-ranging primates are not habituated to human presence. Collecting samples from unhabituated primates is notoriously challenging. Such sampling is possible in cases where primates assemble in large, terrestrial groups(136), but rare for arboreal and cryptic taxa.

Once non-invasive samples have been collected, several challenges must be overcome for population genetics/genomic research. First, non-invasive samples need to be properly preserved for long-term storage, given that primates often reside in remote regions with high temperature and humidity. This usually involves storage in a transportation medium or desiccant (e.g. ethanol, RNAlater, or silica) for weeks or months until they can be frozen. Once samples have

made it to the lab, one must acquire an adequate amount of input DNA. Hair and urine both contain low amounts of total DNA, which can result in poor PCR amplification, allelic dropout, and the inability to generate genomic libraries. In absolute terms, DNA is highly abundant in feces, although the vast majority of it comes from non-endogenous sources such as gut microbes and dietary components(131). Until very recently (see below) working with fecal DNA required the development of highly specific PCR primers to amplify a small number of genetic markers, which often suffered from the same difficulties as other non-invasive biomaterials. Additionally, fecal DNA is usually highly fragmented and degraded, increasing the difficulty of amplification of large targets. Cross-contamination of biomaterial is also a significant problem. In some cases a single hair sample can include hairs from multiple individuals, and fecal samples can come in contact with each other when primates defecate in group settings.

As a result of the considerable difficulty in working with non-invasive biomaterials, the vast majority of such research has focused on primate molecular ecology in the past 20 years, relying upon the amplification of microsatellites, mtDNA, and single genes of interest. While the results of these studies have improved our understanding of conservation concerns, population structure, phylogeography, and adaptation, they remain inherently limited. mtDNA has been invaluable for phylogenetics, but the mitochondrial genome is just a single, uniparentally inherited locus. Microsatellites can be highly informative in the analysis of population structure, landscape genetics, inbreeding, and relatedness, and their fast mutation (slippage) rate allows for the identification of population genetic effects on extremely short time scales (>5 generations(137)). However, in the absence of genomic resources, dozens of microsatellite primers need to be screened for amplification success in a species of interest. Furthermore, the allelic dropout introduced by low endogenous DNA and PCR inhibition, requires that

microsatellites be amplified at least 5 times for accurate fecal genotypes(138). Ultimately, the future of primate conservation genomics will rely on the advancement of nascent laboratory techniques and the coming availability of new genomic resources.

METHODOLOGICAL ADVANCES FOR NON-INVASIVE GENOMICS

The coming advances in primate genomics will to a large degree depend on advances in molecular laboratory techniques for working with degraded and low-quality biomaterials (see Lawler (38) for a similar discussion). The latest extraction and library preparation techniques use single-strand and single-tube approaches that maximize yields from remarkably low inputs(139, 140). Genomic bait-and-capture of endogenous DNA from feces has become an increasingly viable approach to primate genomics(108, 131, 132, 141). This technique involves the generation of DNA or RNA baits, which are hybridized to targeted regions of a primate genome in fecal (i.e. metagenomic) DNA. The resultant "captured" DNA is substantially enriched for endogenous content. While the proportion of non-duplicative on-target reads remains low in comparison to high quality biomaterials like blood and tissue, it allows for the cost-effective genomic sequencing of individual chromosomes or exomes(131, 132, 142). Another promising enrichment technique takes advantage of the different CpG-methylation density between vertebrate and bacterial DNA to selectively capture primate DNA in feces without baits(130), yielding enrichment rates that are comparable to those of bait-and-capture approaches. Methylation-based enrichment has recently been used to analyze genome-wide ancestry and introgression in Kinda and chacma baboons across a hybridation zone(136). Restriction site-associated DNA sequencing (RAD-seq) has been used to reduce genomic complexity for SNP generation in multiple species of primates(136, 143, 144) to study phylogeography, speciation,

and hybridization. Finally, fluorescence-activated cell sorting has recently been used to isolate primate epithelial cells directly from the fecal samples to study population structure and local adaptation in capuchin monkeys(119). In contrast to other techniques, the direct isolation of cells allows for extraction, library preparation, and high-coverage sequencing without any enrichment, and is a promising alternative. Lastly, recent developments have made it possible to selectively sequence in-silico target enriched regions using a handheld portable sequencing device (145, 146). While this technology is still under development, the possibility to perform target enrichment and sequence analysis directly in the field holds tremendous potential.

While the difficulty of obtaining non-invasive samples from unhabituated primates remains, new approaches for sample acquisition have shown substantial promise. Detection dogs have been employed to locate and identify large numbers of fecal samples from multiple species of monkeys and apes(147, 148). These dogs offer the ability to search for the feces of cryptic species without having to locate or disturb the animals themselves, and can be trained in collaboration with police in habitat countries using scat from species of interest(147). The ability to preserve field collected biomaterials has until now required preservation methods that typically yield low quality DNA. Recently, feces collected from free ranging gorillas in the Central African Republic were preserved *in situ* using a portable freezer attached to a solar powered battery, which allowed for the study of gene expression with RNA-seq(149). Such an approach could also be used to preserve other biomaterials for molecular work that requires high quality DNA. In addition to fecal sampling, progress has been made in the use of alternative biomaterials. In particular, urine shows exceptional promise(134) for primate genomics. Unlike feces, the DNA derived from urine is almost entirely of an endogenous source. Ozga *et al*.(134) successfully sampled urine from chimpanzees at Gombe, which after the application of genomic

capture methods, mapped with high efficiency to a chimpanzee reference genome. Sampling protocols can also be tailored to the behavior of the target species. For example, Aye-ayes forage for larvae by gnawing and digging into trunks and branches of trees. Aylward *et al*.(150) successfully harvested saliva from these feeding traces for population genetic monitoring. Further creative advances in non-invasive sampling are undoubtedly on the horizon.

THE FUTURE OF PRIMATE CONSERVATION GENOMICS

Primate conservation genomics is at the dawn of a new era. Developments in field and laboratory biology are being fueled by the rapid expansion of low-cost genome sequencing options. As these recent methodological advances demonstrate, the technical foundations for robust and widespread primate conservation genomics are present. However, the extent to which these approaches have been implemented has been hindered by the limited availability of genomic resources and the high cost of sequencing. Given that the cost-prohibitive barrier of genome sequencing has been broken, we expect that in the near-term future the release of new primate reference genomes across the primate order will be coupled with expansive blood- and tissue-based resequencing efforts. Assuredly, this forthcoming first wave will reveal tantalizing new insights into genomic diversity, population history, genetic load, species boundaries, and adaptation across the primate order.

However, it remains the case that the vast majority of the world's primate genomic diversity exists within free-ranging primates and is only accessible via non-invasive means. The key to unlocking genome-informed primate conservation will be the integration of new non-invasive techniques with newly available genomic resources and low cost sequencing. As such, we expect that a second wave of primate conservation genomics will bring about the sequencing

of large populations of primates from multiple sites and different ecological settings. This new reality will allow for fine-grained assessments of population genetic diversity, gene flow, and inbreeding across variable geographic scales. We also expect that it will become more common to couple the sequencing of modern genomes with those derived from historical and museum specimens. Genomic capture approaches are suitable for both types of biomaterials in the absence of low-cost brute force sequencing. Such an approach allows for a deeper understanding of how genomic diversity has been shaped and lost within species over the course of population declines that are likely the result of anthropogenic effects. Depending on the quality of museum records, it can also be possible to target a modern/historic approach to a fine scale within specific geographic regions. Further studies could examine the role of local adaptation in population viability. Most primates occupy highly fragmented habitats, and/or belong to small populations. As such, drift could be having exaggerated effects in some populations or species thereby influencing survival.

Given the coming extinction crisis faced by the world's primates, we suggest that the wide scale application of genomics to primate conservation is not only possible, it is essential. The availability of cheap sequencing has now made it possible for genomics to facilitate informed conservation cost-effectively. However, it will be critical to apply these new tools rapidly and targeted toward the areas and species of greatest need. We call particular attention to the primates of Madagascar where habitat fragmentation and deforestation have put a staggering 87% of species at risk of extinction. Furthermore, given their phylogenetic distance from humans, they have received only limited attention from the genomics community. In spite of this, lemurs are extraordinarily diverse not just taxonomically, but also morphologically and behaviorally. A deeper understanding of lemur genomics would not only have conservation

merit, but also provide a major new source of biomedical and evolutionary information relevant to humans.

DISCLOSURE STATEMENT

The authors declare no conflict of interest that might affect this review.

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FIGURES

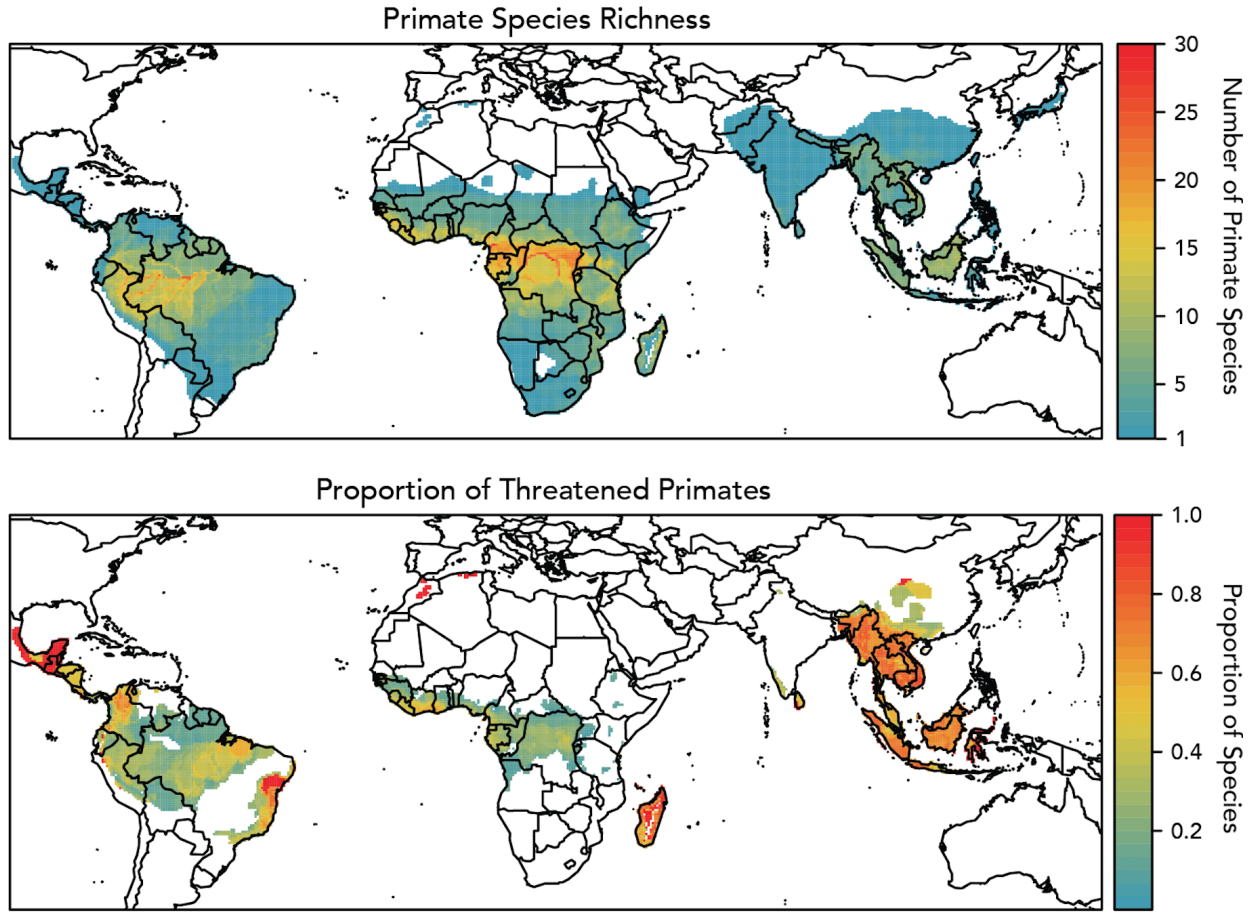

Figure 1: Top: Global map of primate species richness in 0.5° grids. Species range data from IUCN red list version 6.2. Bottom: Proportion of species that are threatened according to the IUCN (VU,EN,CR).

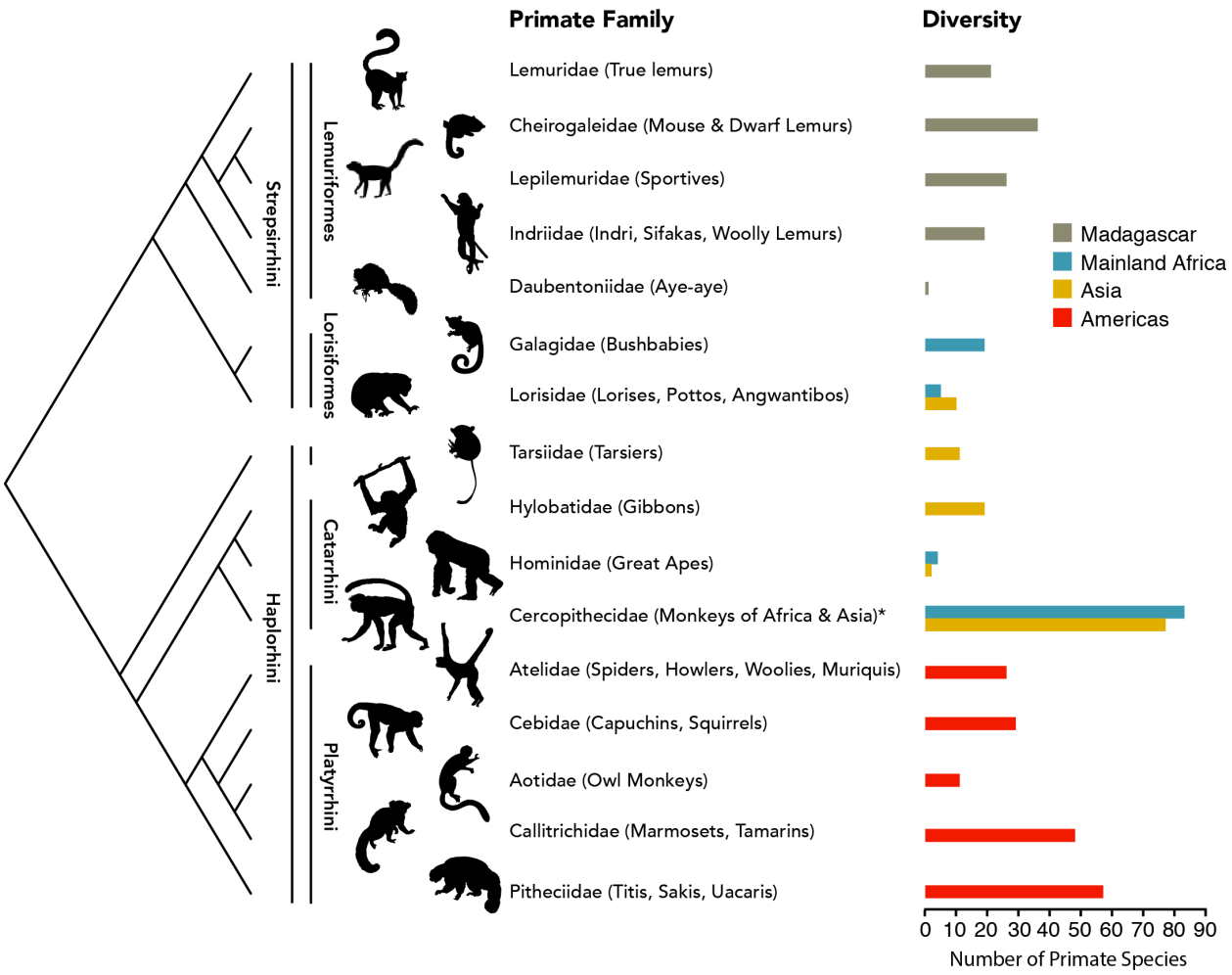

Figure 2: Left: cladogram of primate families. Right: Number of species per family present in each of the four major primates geographic ranges, with data from (30). *Major groups of cercopithecidae include Baboons, Geladas, Swamp Monkey, Talapoins, Patas, Vervets, Mangabeys, Geladas, Guenons, Kipunji, Drill/Mandrill, Macaques, Langurs, Doucs, Snub-Noses, Proboscis, Colobus, Langurs, and Surilis. Silhouettes acquired from Phylopic.org used under a creative commons license