Harvesting the fruits of the first stage of the Primate Genome Project

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Primates are highly successful mammals with significant morphological, behavioral, and physiological diversity. Studying the genomes of non-human primates, as the closest relative of humans, can provide insights into human evolution, genetic structure, and potential drug targets relevant to human health, thus making important contributions to medical research. Additionally, primate genome research can support ecological balance and resource conservation and promote sustainable development and human well-being. Despite the existence of more than 500 primate species belonging to 80 genera and 16 families worldwide, with new species still being discovered in recent years (Fan et al., 2017; Khanal et al., 2021; Roos et al., 2020), genome sequencing efforts have been limited to a relatively small number of species from only 22 genera (Ensembl v103). Notably, approximately 72% of primate genera remain unsequenced, leading to significant knowledge gaps in our understanding of their evolutionary history. This situation presents considerable challenges for the development, utilization, and protection of primate genetic resources. It is for these compelling reasons that we initiated the Primate Genome Project (PGP) (Wu et al., 2022).

In the first stage of the PGP, we aimed to sequence the genomes of 27 primate species using long-read sequencing technologies. This expansion of high-quality reference genomes will provide crucial information for comparative primate phylogenomics and for the reconstruction of the primate tree of life, thereby elucidating the genomic changes underlying the speciation and adaptation processes of major primate lineages.

The project involved sequencing high-quality reference genomes of 27 primate species, including previously unexplored basal lineages, using long-read sequencing technologies. These genomes were combined with 23 previously published primate and outgroup genomes to conduct a systematic phylogenomic analysis of 50 primate species from 38 genera and 14 families to gain insights into their genomic and phenotypic evolution (Shao et al., 2023). Based on 433.5 Mbp of gap-free homologous sequences from the 50 primate species and two outgroups, we constructed a new high-resolution primate genome phylogeny. The improved dating calibrations estimated the emergence of crown Primates to between 64.95 and 68.29 million years ago, coinciding with the Cretaceous/Tertiary boundary. Analysis of genome structural evolution revealed a generally conserved history of karyotype evolution from the common ancestor of primates to humans, as well as heterogeneous rates of genome rearrangement and gene evolution across primates (Shao et al., 2023). Based on large-scale systematic genomic analysis, the evolutionary history of primate genomes was reconstructed, providing insights into the genomic mechanisms underlying important phenotypic innovations in different evolutionary lineages.

In genome evolution, chromosomes X and Y exhibit notable differences from autosomes. The Y chromosome, in particular, has been subjected to distinct selective pressures. It contains the pseudo-autosomal region, which is shared with the X chromosome, as well as a non-recombining male-specific region, which has experienced extensive gene loss in comparison to other genomic regions, often accompanied by the accumulation of repetitive sequences (Bachtrog, 2013). Leveraging long-read sequencing technology to assemble and refine the Y chromosomes across 19 primate species, we tripled the number of existing Y chromosome assemblies in primates from 10 to 29, covering all major lineages. We found that the pseudo-autosomal boundary has shifted at least six times during primate evolution, leading to the formation of one evolutionary stratum specific to Simiiformes and the independent emergence of young strata in Catarrhini and Platyrrhini (Zhou et al., 2023). In addition, different primate lineages have experienced different rates of gene loss, structural changes, and lineage-specific amplifications within their Y chromosomes, reflecting unique evolutionary trajectories. Significant differences in X and Y chromosomal conformation were also observed, which may be associated with the structural variations in Y chromosomes. Lastly, lineage-specific amplifications in ampicionic regions further increased the diversity in Y chromosome structure and composition (Zhou et al., 2023). These findings fill important phylogenetic gaps in primate Y chromosome evolution and expand our understanding of the structure and genetic characteristics of primate sex chromosomes.

During hominid evolution, incomplete lineage sorting (ILS) occurred extensively in the genomes of the great apes, exerting a profound influence on human evolutionary history (Patterson et al., 2006). To expand our understanding of ILS across 29 major ancestral nodes within the primate system and infer accurate genome regions, Rivas-González et al. (2023) utilized a hidden Markov model approach and revealed that up to 64% of the genome has been impacted by ILS at individual nodes. ILS exhibits extensive variation along the genome, primarily driven by recombination. However, due to the significant impact of selection on genomic variation, intrinsic ILS near genes is more strongly affected by linked selection than intergenic ILS. As a result, distance to genes...
also influences ILS. Interestingly, Rivas-González et al. (2023) also observed a greater reduction of ILS on the X chromosome compared to autosomes, indicating a heightened impact of natural selection on X chromosome across multiple nodes. Notably, their analyses revealed that genes with significant ILS are enriched in immune functions, while those genes with relatively low ILS tend to exhibit “housekeeping” functions. Overall, the widespread presence of ILS among primates underscores species-specific selection and shared selection targets.

Hybridization between species, leading to the emergence of a new species, is a remarkable mechanism of speciation and has long intrigued evolutionary biologists (Taylor & Larson, 2019). Wu et al. (2023) and Zhang et al. (2023) both discovered historic hybridization events in the Rhinopithecus and Macaca genera, respectively, resulting in the formation of hybrid species. Within Rhinopithecus, Wu et al. (2023) found that the geographically isolated R. brelichi (gray snub-nosed monkey) exhibits a stable mixed genomic ancestry derived from R. roxellana (golden snub-nosed monkey) and the ancestor of R. bieti (black-white snub-nosed monkey) and R. strykeri (black snub-nosed monkey). They further identified critical genes originating from each parental lineage that may be involved in the formation of the distinctive coat coloration in R. brelichi, potentially accelerating pre-mating isolation between hybrids and parental lineages. In addition, they found alternately inherited alleles of multiple reproduction-related genes in R. brelichi that may have caused post-mating reproductive isolations (RIs). They outlined a comprehensive evolutionary scenario, detailing the progression from genomic admixture to the establishment of RIs through the alternate inheritance of divergent alleles from parental lineages (Wu et al., 2023). Within Macaca, Zhang et al. (2023) found that the fascicularis group of macaques originated from an ancient hybridization event between the sinica and silenus groups approximately 3.45–3.56 million years ago. The X-chromosomes and low-recombination regions exhibited equal contributions from each parental lineage, suggesting they were less affected by subsequent backcrossing and may have played an important role in maintaining hybrid integrity. They also identified multiple reproductive-related genes that may contribute to the development of the hybrid sexual phenotype observed in the fascicularis group macaques (Zhang et al., 2023). These studies offer genomic-based approaches and methodologies that can be used to identify both known and unknown hybrid species, while emphasizing the often-underappreciated impact of hybridization on the generation of species and phenotypic diversity in mammals (Wu et al., 2023; Zhang et al., 2023).

Primates display a wide range of phenotypes unique to their respective lineages. The genetic mechanisms that underlie this phenotypic variation, however, remain largely unknown. We reported genomic innovations occurring at the ancestral nodes of Simiiformes and further identified candidate genes under positive selection in different lineages. These genes may play roles in the neural, skeletal, digestive, and sensory systems, potentially contributing to primate evolution, innovation, and adaptation (Shao et al., 2023). Our research focused on the slow loris, a suborder of primates within Strepsirrhini, which exhibits distinct physiological and

Figure 1  Schematic summary of the findings of the first stage of the Primate Genome Project
behavioral traits throughout its evolutionary history, including low metabolic rate, slow movement, and nocturnal behavior. To explore the genetic mechanisms underlying their adaptive evolution, we assembled a chromosome-level reference genome sequence for the pygmy slow loris (Nycticebus pygmaeus) and performed whole-genome resequencing on 50 pygmy slow lorises and six Bengal slow lorises (Nycticebus bengalensis). Our findings revealed an expansion of the GSTA gene family, which is associated with detoxification, in slow lorises (Li et al., 2022). Furthermore, we observed a decrease in the enzymatic activity of the PITRM1 gene, exhibiting convergent evolution with koalas, suggesting its potential contribution to their low metabolic rate. In addition, we identified two positively selected genes, MYOF and PER2, which may be linked to their slow movement and unusual circadian rhythms (Li et al., 2022).

Primates have successfully diversified their social systems throughout evolution. However, the biological mechanisms responsible for this phenomenon are still not well understood. Asian colobine monkeys provide a suitable model for studying primate social evolution, as they have undergone a staged process of social evolution from a one-male multi-female unit to complex multi-level social structures. We established a social-ecological-genomic framework of primates by integrating genomic information, paleogeographic data, fossil records, niche modeling, and behavioral analysis. Our results showed that primate species inhabiting colder environments tend to reside in larger groups (Qi et al., 2023). Ancient ice ages played a critical role in the social evolution of these primates, promoting the aggregation of northern odd-nosed monkey species into nested multi-level social forms. During this process, many genes related to cold adaptation and the nervous system underwent positive selection in these monkeys. Specifically, these species developed more efficient dopamine (DA) and oxytocin (OXT) pathways to cope with cold stress, leading to prolonged maternal care and nursing to enhance offspring survival in cold environments. These adaptive changes resulted in strengthened intra-individual connections, male neighbor tolerance, and cooperation, ultimately facilitating a staged convergence from independent one-male multi-female units to multi-level societies. Furthermore, in vitro experiments demonstrated increased binding efficiency of DA/OXT receptors associated with larger group sizes in these species. Consistently, behavioral analyses indicated significantly higher social interactions among these species, such as grooming and inter-family engagement (Qi et al., 2023). This study represents the most comprehensive research conducted to date on animal social evolution, providing new insights and paving the way for further exploration in the field of social evolution.

Changes in regulatory regions have fewer pleiotropic effects than changes in coding sequences, and hence are more likely to give rise to significant phenotypic effects (Wray, 2007). The contribution of regulatory element changes to long-term evolution and phenotypic diversity across lineages remains largely unexplored. We provided a comprehensive landscape of lineage-specific accelerated regions (LinARs) across primate evolution and found that over 77% of LinARs in 49 primate species overlapped with long non-coding RNA or cis-regulatory elements, indicating functional significance in the primate genome. We updated the LinARs in humans and found over 1,000 previously undetected fast-evolving sequences in the human genome, many of which are associated with genes relevant to brain development or disease. Functional experiments indicated that the first eight human LinARs functioned as long non-coding RNAs highly expressed in the human motor cortex. Other non-human primates have also demonstrated fascinating phenotypic adaptations. Notably, in vitro studies have shown that LinARs from two great ape species (with significantly elongated arms) may participate in the regulation of their unique limb structures, whilst some LinARs in Colobinae are associated with detoxification, which may contribute to their adaptation to a leaf-eating diet (Bi et al., 2023).

In summary, the initial stage of the PGP involved the sequencing of 27 primate species using advanced sequencing technologies, thereby expanding the number of high-quality reference genomes. These high-quality genomes serve as a valuable tool for comparative primate systematics, reconstructing the primate tree of life, and elucidating genomic changes underlying speciation and adaptation in major primate lineages. Furthermore, the above studies on primate social evolution, hybridization, regulatory element modifications, and the genetic mechanisms underlying distinctive phenotypic traits contribute to a more comprehensive understanding of primate evolution and diversification. Overall, the PGP not only contributes to medical research, but also plays a vital role in supporting ecological balance, conserving resources, promoting sustainable development, and enhancing human well-being.

The second stage of the PGP will focus on both depth and breadth. Firstly, we will expand the range of genome sequencing to cover more primate genera through the collection of additional samples. Secondly, using advanced sequencing technologies and multiomics data, such as transcriptomics and epigenetics, we will obtain higher quality and more comprehensive data. We will also conduct further experiments to explore the functions of candidate genes and genomic elements identified during this stage, and explore their effects on phenotypic formation, species diversity, and human diseases. Finally, we will also investigate the regulatory mechanisms of primate-specific phenotypes and behaviors in different evolutionary groups to understand the interactions between genotype and phenotype. Taken together, these efforts will contribute to a more holistic understanding to the genomic and phenotypic evolution of primates, including humans.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS’ CONTRIBUTIONS

X.G.Q., D.D.W., G.Z., and L.Y. conceived the draft. Y.T.G. wrote the draft materials. All authors contributed to the discussions. All authors read and approved the final version of the manuscript.

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REFERENCES


