American Journal of Primatology

WILEY

AMERICAN JOURNAL OF PRIMATOLOGY

REVIEW ARTICLE OPEN ACCESS

Recent Insights Into the Evolutionary Genomics of the Critically Endangered Aye-Aye (*Daubentonia madagascariensis*)

Vivak Soni | Susanne P. Pfeifer | Jeffrey D. Jensen

School of Life Sciences, Center for Evolution and Medicine, Arizona State University, Tempe, Arizona, USA

Correspondence: Susanne P. Pfeifer (susanne@spfeiferlab.org) | Jeffrey D. Jensen (jeffrey.d.jensen@asu.edu)

Received: 5 October 2025 | **Revised:** 30 November 2025 | **Accepted:** 7 December 2025

Funding: National Institute of General Medical Sciences, Grant/Award Numbers: R35GM151008, R35GM139383

Keywords: aye-aye | *Daubentonia madagascariensis* | Daubentoniidae | population genetics | primate | strepsirrhine

ABSTRACT

Endemic to the island of Madagascar, the enigmatic aye-aye is amongst the most endangered primates on the planet. Due to their nocturnal and arboreal lifestyle and large geographic ranges, much remains unknown about these lemurs. The publication of a recent high-quality reference assembly with gene-level annotations, together with whole-genome population-level sequencing data, has facilitated a number of studies modeling the fundamental evolutionary processes shaping the patterns and levels of genetic variation in aye-ayes. In this review, we survey these recent findings, highlighting new insights into the selective and demographic history of the species, as well as into genome-wide patterns of mutation and recombination as assessed from both pedigree-based and divergence-/polymorphism-based analyses.

1 | Introduction

First described in 1780 by the French zoologist Louis J. M. Daubenton (Gotch 1995), the aye-aye (*Daubentonia madagascariensis*) is 1 of over 100 species of lemur endemic to Madagascar (IUCN 2024), an island maintaining one of the highest levels of unique biodiversity across the globe. Aye-ayes are perhaps best known for their highly unusual anatomical features specialized for extractive foraging, including continuously growing incisors used to gnaw through tree bark, an elongated middle digit for extracting insect larvae, and the largest relative brain size amongst strepsirrhines (Cartmill 1974; Martin 1990; Simons 1995). As the sole extant member of the Daubentoniidae family, a lineage for which the last common ancestor with humans was approximately 53.8–74.7 million years ago (mya; Yoder 1997; Horvath et al. 2008; Perelman et al. 2011; McLain et al. 2012)—with recent evidence supporting that lower bound (Soni, Versoza, Terbot, et al. 2025)—aye-ayes therefore represent a relatively basal primate split. This unique position renders this charismatic species of considerable evolutionary interest.

The rapid deforestation characterizing recent decades in Madagascar has contributed to severe population decline in aye-ayes (Louis et al. 2020; Suzzi-Simmons 2023). Consequently, the species is now amongst the 25 most endangered primates in the world, with fewer than 1000–10,000 individuals estimated to remain in the wild according to the International Union for Conservation of Nature (IUCN) and the Natural Resources Species Survival Commission Primate Specialist Group (Schwitzer et al. 2013; Louis et al. 2020; and see the discussion in Gross 2017). Given their large individual home ranges relative to other lemurs (Ganzhorn et al. 1985; Schülke 2005; Benadi et al. 2008; Volampeno et al. 2011), low population densities (Mittermeier et al. 2010), and amongst the lowest genetic diversity of any primate measured to date (Kuderna et al. 2023), the fragmentation and erosion of their habitat puts aye-ayes at considerable risk of extinction. Initial estimates of

Summary

- Recent research has elucidated the evolutionary genomics of aye-ayes, following the publication of a high-quality, annotated reference assembly and whole-genome polymorphism data.
- Results suggest a demographic history shaped by anthropogenic influences, as well as the action of positive and balancing selection targeting sensory-related genes.
- Both pedigree-based direct approaches and divergence-/polymorphism-based indirect approaches have quantified mutation and recombination processes in the species, providing one of the first estimates in strepsirrhines.

genetic diversity in the species as a whole ranged from 0.051% based on heterozygous sites within a single individual genome (Perry, Melsted, et al. 2012) to 0.073% based on synonymous sites within transcriptome data of 1175 genes from 2 individuals (Perry, Reeves, et al. 2012). Though the aye-aye's range covers the North–South axis of Madagascar, the species' arboreal lifestyle restricts their range to the rainforests found in the north, east, and central west of the island, and dry forests in the west (Sterling 1994; Louis et al. 2020). This geography has resulted in appreciable levels of genetic structuring, with initial diversity levels estimated from low-coverage synonymous site data (Perry et al. 2013) being consistent with the species-wide estimates (with the Northern [$n = 4$], Eastern [$n = 5$], and Western [$n = 3$] populations estimated at 0.054%, 0.057%, and 0.049%, respectively).

These early estimates of genetic diversity were the result of a series of studies which generated the first draft genome assembly (DauMad_1.0, based on ~20× coverage 100 bp paired-end Illumina Genome Analyzer IIx sequence data; Perry, Reeves, et al. 2012) and population genomic data (Perry, Melsted, et al. 2012; Perry et al. 2013) in aye-ayes. In addition to measures of genetic diversity, Perry et al. (2013) described high levels of population differentiation between the Northern and Eastern populations, despite their being separated by < 250 km, positing the existence of a long-term barrier to gene flow. Updated assemblies for the species were published in 2020 (DauMad_v1_BIUU, based on ~75× coverage 250 bp paired-end Illumina HiSeq 2500 sequence data; Zoonomia Consortium 2020) and 2023 (ASM2378347v1, based on ~60× coverage PacBio RSII sequence data; Shao et al. 2023), though the latter was at the contig-level, whilst previous assemblies were at the scaffold-level. The most recent and highest quality assembly to date (DMad_hybrid) is based on a sample from a female aye-aye housed at the Duke Lemur Center, and was generated using a combination of Oxford Nanopore Technologies long reads and Illumina short reads and scaffolded using chromatin conformation data (Versoza and Pfeifer 2024). Table 1 compares the contiguity and completeness of these aye-aye genome assemblies.

Importantly, the genomic assembly of Versoza and Pfeifer (2024) is the first with protein-coding gene annotations, facilitating the potential for inference of various neutral and selective population genomic processes and their relative effects on genetic variation. More specifically, it is well established that different evolutionary processes can produce similar patterns and levels of genetic variation, making it frequently difficult to distinguish amongst them. For instance, demographic change can confound and bias the inference of natural selection, and vice versa (e.g., B. Charlesworth et al. 1993; B. Charlesworth 1996, 2013; Jensen et al. 2005; Kaiser and Charlesworth 2009; O'Fallon et al. 2010; Crisci et al. 2012, 2013; Zeng 2013; Poh et al. 2014; Ewing and Jensen 2016; Harris and Jensen 2020; Johri et al. 2021; Jensen 2023; Soni et al. 2023; Soni, Terbot, Jensen 2024; Soni and Jensen 2025). Recent studies have therefore highlighted the need for an evolutionarily appropriate baseline model (Johri, Eyre-Walker, et al. 2022; Johri, Aquadro, et al. 2022) that incorporates constantly operating processes such as genetic drift (as modulated by population history), variation in mutation and recombination rates, and purifying and background selection (BGS) effects. With such a model acting as the "null" expectation, one can more accurately identify rare evolutionary events such as recent positive and balancing selection. To generate a baseline model as described, however, one requires information on where such processes are occurring in the genome, and thus, protein-coding gene annotations are necessary. For example, knowledge of the location of functional elements enables the identification of genomic regions in which purifying selection and BGS are operating, allowing for an accounting of these processes in the baseline model. Furthermore, protein-coding gene annotations are naturally of great value for performing genomic scans to identify recent targets of positive or balancing selection.

The annotated assembly of Versoza and Pfeifer (2024), combined with subsequent high-quality, whole-genome, population-level sequencing, has thus facilitated the detailed inference of population genomic processes in aye-ayes. This

TABLE 1 | Published aye-aye genome assemblies.

	DauMad_1.0	DauMad_v1_BIUU	ASM2378347v1	DMad_hybrid
Study	Perry, Reeves, et al. (2012)	Zoonomia Consortium (2020)	Shao et al. (2023)	Versoza and Pfeifer (2024)
NCBI accession no.	GCA_000241425.1	GCA_004027145.1	GCA_023783475.1	GCA_044048945.1
Assembly level	Scaffold	Scaffold	Contig	Scaffold
Gene annotation	No	No	No	Yes (18,858 genes)
Complete BUSCOs (primates)	12.96%	90.31%	94.46%	99.19%

Note: The BUSCO (Benchmarking Universal Single-Copy Orthologs) score is a quantitative assessment of the completeness of a genome assembly.

inference has included improved estimates of population history, sex-specific pedigree-based and fine-scale divergence-based mutation rates, as well as sex-specific pedigree-based and fine-scale polymorphism-based crossover (CO) and non-crossover (NCO) recombination rates, the characterization of the distribution of fitness effects (DFE) of new mutations in coding regions, and the identification of genomic regions targeted by the recent action of positive and balancing selection. In this review, we summarize these recent advances in aye-aye population genomics, interpret these estimates within a comparative primate framework, and discuss their implications for future conservation management of this critically endangered species.

2 | Direct and Indirect Estimates of Mutation Rates

Germline mutations are the ultimate source of novel genetic variation within and between species. Research over recent decades has revealed that mutation rates are highly variable, exhibiting differences across multiple biological scales. These differences occur within genomes (between specific sites), among individuals in a population, between populations of the same species, and across species (see the reviews of Baer et al. 2007; Lynch 2010; Hodgkinson and Eyre-Walker 2011; Pfeifer 2020a). Thus, quantification of the rate and variability in the input of new mutations is fundamental to understanding patterns and levels of genetic variation. Although it is common practice to utilize a single, species-averaged mutation rate when constructing evolutionary models, failing to account for the heterogeneity in mutation rate can result in misinference in downstream analyses, as has recently been demonstrated for the inference of both population history and the DFE (Soni, Pfeifer, et al. 2024; Soni and Jensen 2025; and see Ghafoor et al. 2023).

2.1 | Inferring Mutation Rates From Population Genomic Data

Broadly speaking, mutation rate inference strategies in large organisms such as primates fall into the categories of direct or indirect inference approaches (though note that in humans, disease incidence approaches [e.g., Haldane 1932, 1935] were largely used prior to the advent of DNA sequencing technologies). Given that selectively neutral mutations (i.e., those that do not impact fitness) are expected to occur at a rate that is relatively constant over short to moderate evolutionary timescales, the degree of neutral genetic divergence between two species is expected to be directly correlated with the time elapsed since their last common ancestor (though see Moorjani et al. 2016). The theoretical underpinnings of this Molecular Clock hypothesis were posited by *The Neutral Theory of Molecular Evolution* (Kimura 1968, 1983), and—since the advent of genome sequencing—have been used to indirectly infer mutation rates from species-level divergence data in a wide range of organisms (e.g., between humans and chimpanzees; Nachman and Crowell 2000; The Chimpanzee Sequencing and Analysis Consortium 2005). Specifically, mutation rates averaged across time can be inferred from phylogenetic sequence data in neutrally evolving genomic regions, given that the per-generation mutation rate μ is equal to the substitution rate (Kimura 1968, 1983).

As these indirect approaches therefore require neutrally evolving sites, it is necessary to mask functional regions from such analyses. To date, high-quality annotated genomes are available for a relatively small number of organisms. Furthermore, numerous factors impact local genomic mutation rates, including GC-content (Hwang and Green 2004), the recombination landscape (Agarwal and Przeworski 2019), as well as more general life history traits (see the discussion of Tran and Pfeifer 2018). Moreover, uncertainties in divergence and generation times must be considered, and therefore indirect mutation rates will generally be given as a range accounting for the degree of these uncertainties. That said, an important advantage of such indirect inference approaches is that mutation rates can be calculated across genomic windows, facilitating the fine-scale mapping of mutation rate heterogeneity across the genome in a way that is generally not feasible with direct approaches. Because mutation rate heterogeneity can bias the inference of both demographic and selective histories if unaccounted for (Soni, Pfeifer, et al. 2024), these fine-scale mutation rate maps are an important feature of any evolutionary baseline model.

By contrast, the direct estimation of mutation rates via observation of de novo mutations (DNMs) in parent–offspring trios has become a viable approach given the reduction in sequencing costs, as well as the development of novel computational pipelines necessary to identify genuine DNMs (see the review of Pfeifer 2020a). As the name suggests, the number and distribution of spontaneous mutations occurring in the offspring relative to the parental generation are directly observed, and as such this approach is not dependent upon divergence- or generation-time assumptions as is the case with indirect approaches. This advantage, however, is also a trade-off in that such approaches track mutations over short evolutionary timescales (i.e., a small number of generations). Across such timescales, DNMs are extremely rare in primates. This means that fine-scale genomic rate mapping is generally not feasible, given that relatively few mutations can be observed across the entire genome in a given pedigree. Moreover, sequencing error rates are generally much higher than the spontaneous mutation rate itself. Therefore, a central challenge of direct mutation rate estimation lies in identifying these sequencing errors in order to avoid their misidentification as DNMs (Pfeifer 2017a). Although experimental validation via orthogonal sequencing technologies can aid in the reduction of the false positive rate, this approach necessitates additional sequencing which is often problematic due to the limited samples available for many species, in particular those of conservation concern. An alternative strategy involves the application of carefully selected statistical filter criteria as part of a computational pipeline in order to remove false positives. Such computational approaches necessitate caution though, as genuine DNMs may also be lost with stringent filtering (Ségurel et al. 2014), and it is therefore necessary to infer both the false-positive and false-negative rates of the experiment, which can prove challenging (Pfeifer 2017b).

2.2 | Direct Pedigree-Based Estimates of the Germline Mutation Rate in Aye-Ayes

Recent years have witnessed the quantification of DNMs in humans and numerous nonhuman primates (Roach et al. 2010; Conrad et al. 2011; Campbell et al. 2012, 2021; Kong et al. 2012; Michaelson et al. 2012; Venn et al. 2014; Francioli et al. 2015; Besenbacher

et al. 2016, 2019; Goldmann et al. 2016; Rahbari et al. 2016; Wong et al. 2016; Jónsson et al. 2017; Pfeifer 2017b; Tatsumoto et al. 2017; Thomas et al. 2018; Sasani et al. 2019; Kessler et al. 2020; Wang et al. 2020; Wu et al. 2020; Bergeron et al. 2021, 2023; C. Yang et al. 2021), revealing substantial—though < 10-fold—variation in mutation rates between species, and lower rates in strepsirrhines (see the reviews of Tran and Pfeifer 2018; Chintalapati and Moorjani 2020). Earlier this year, Wang et al. (2025) performed a direct estimation of the mutation rate in aye-ayes from DNMs identified in 12 trios, finding, unexpectedly, a female mutation bias. Notably though, this observation was driven by only three individuals, all of which harbored a much larger number of DNMs (83, 108, and 117 DNMs) than the remaining individuals included in the study (median: 30 DNMs). As such, this conclusion—which is in contrast to multiple findings of male-biased mutation in other primate species, and across amniotes in general (e.g., Kong et al. 2012; Venn et al. 2014; Wong et al. 2016; Jónsson et al. 2017; Thomas et al. 2018; Besenbacher et al. 2019; Sasani et al. 2019; Wu et al. 2020; Bergeron et al. 2021)—should be interpreted with great caution. In fact, once these three individuals were excluded from their study, the authors observed a male mutation bias (α) in aye-ayes that is within the range of those observed in other mammals ($\alpha = 2.82$; Wang et al. 2025).

Concurrently, another pedigree-based study was conducted by Versoza, Ehmke, et al. (2025), based on whole-genome sequencing of seven trios from a three-generation pedigree. Although smaller in sample size, the study included a wide range of parental ages (from 7.4 to 26.5 years old). Given that aye-ayes have a reproductive lifespan that ranges from 30 months to over 30 years of age, this wide age range provided valuable insights into the impact of parental age on mutation rates in the species. In order to address the challenges of identifying DNMs described in the above section, Versoza, Ehmke, et al. (2025) developed a computational pipeline based on the pan-genome approach of Eggertsson et al. (2017), and then visually inspected candidate DNMs for errors related to sequencing, read mapping, variant calling, and genotyping. A total of 323 DNMs passed 2 rounds of visual inspection, with the majority found within intergenic and intronic regions as expected from the overall genome composition. Consistent with previous studies, Versoza, Ehmke, et al. (2025) found that the per-site, per-generation germline mutation rate increased with parental age (maternal age: $r^2 = 0.7440$ at $p < 0.005$; paternal age: $r^2 = 0.5936$ at $p < 0.05$). The mean inferred mutation rate was 1.1×10^{-8} per base pair per generation (/bp/gen), with rates ranging from 0.4×10^{-8} (maternal age = 9.2 years; paternal age = 11.2 years) to 2.0×10^{-8} (maternal age = 26.5 years; paternal age = 24.4 years) across the studied trios. As the age of reproduction in the wild likely tends toward younger parents, this lower estimate may be the more appropriate for evolutionary studies. Contrary to the Wang et al. (2025) study discussed above, Versoza, Ehmke, et al. (2025) observed a male mutation bias of between 2.6 and 2.8 in aye-ayes, consistent with other primate species (Bergeron et al. 2023). Figure 1 compares the germline mutation rate in aye-ayes with those

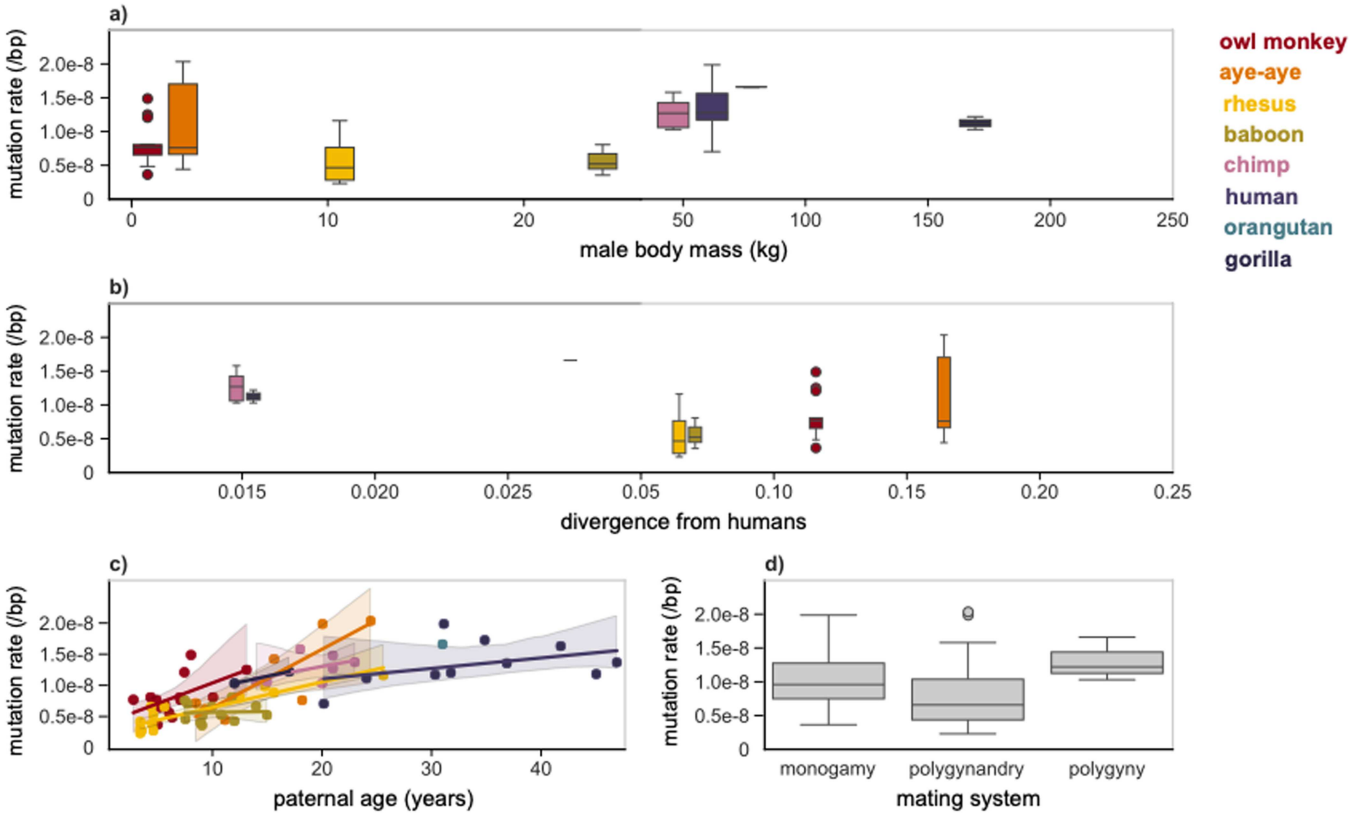

FIGURE 1 | Primate germline mutation rates plotted against (a) male body mass; (b) divergence from humans; (c) paternal age; and (d) mating system. Germline mutation rates and paternal age were obtained from Jónsson et al. (2017) for humans; Tatsumoto et al. (2017) for chimpanzees; Besenbacher et al. (2019) for gorillas and orangutans; Wu et al. (2020) for baboons; Bergeron et al. (2021) for rhesus macaques; Thomas et al. (2018) for owl monkeys; and Versoza, Ehmke, et al. (2025) for aye-ayes. Male body masses were obtained from Smith and Jungers (1997). Estimates of divergence from humans were obtained from the 233-way primate alignment of Kuderna et al. (2023), updated with the aye-aye genome of Versoza and Pfeifer (2024).

estimated in numerous other primates, with mutation rates plotted against body mass, divergence, parental age, and mating system.

2.3 | Indirect Divergence-Based Estimates of the Fine-Scale Mutation Rate in Aye-Ayes

Unlike pedigree-based approaches for mutation rate estimation, indirect approaches track mutations over much longer evolutionary timescales and are therefore suitable for generating fine-scale maps of the mutation rate across the genome, as discussed above. To infer mutation rate maps in aye-ayes, Soni, Versoza, Terbot et al. (2025) calculated the divergence along the aye-aye branch by replacing the outdated aye-aye genome in the 447-way multiple species alignment (Zoonomia Consortium 2020; Kuderna et al. 2023) with the high-quality, chromosome-level genome assembly of Versoza and Pfeifer (2024), and counting fixations along this branch. Crucially, because the updated aye-aye genome is annotated at the gene level, the authors were able to mask functional regions in order to avoid the potentially confounding effects of selection. Mutation rates could then be calculated across genomic windows, considering a likely range of possible generation times in aye-ayes and divergence times of the aye-aye branch. Utilizing previous estimates of generation times in aye-ayes of between 3 and 5 years (Ross 2003; Louis et al. 2020), and divergence times ranging from 54.9 to 74.4 mya (Horvath et al. 2008), Soni, Versoza, Terbot, et al. (2025) inferred a mutation rate map with a mean, fine-scale, autosomal mutation rate of between 0.173×10^{-8} and 0.393×10^{-8} /bp/gen. Additionally, Soni, Versoza, Terbot, et al. (2025) utilized the pedigree-based mutation rates inferred by Versoza, Ehmke, et al. (2025), in order to infer divergence times. Given the wide range of parental ages in the pedigrees, this yielded divergence times spanning from 53.8 to 6.45 mya. This supports the likelihood of a younger mean age of reproduction, as the more recent portion of this divergence range (corresponding to older parents) is incompatible with the fossil record, which has been interpreted to suggest a split ~55 mya (Hartwig 2011).

Taken together, there is thus an encouraging convergence between different mutation rate inference approaches in aye-ayes. First, the earliest divergence time of 53.8 mya based on the pedigree-based mutation rates of Versoza, Ehmke, et al. (2025) from young parents corresponds well with the fossil record and with the likely split of this branch near the time of origin of primates (Tavaré et al. 2002; Zhang et al. 2008; and see Pozzi et al. 2014). Second, the indirectly estimated mutation rate corresponding to this divergence time aligns with the directly inferred mutation rate from young parents, suggesting $\sim 0.4 \times 10^{-8}$ /bp/gen to be a well-supported mean autosomal mutation rate in aye-ayes.

Finally, Terbot, Soni, Versoza, Milhaven, et al. (2025) applied the approach of Soni, Versoza, Terbot, et al. (2025) outlined above to additionally study the fine-scale mutation rate on the X chromosome in aye-ayes. They inferred a mean mutation rate of 0.378×10^{-8} /bp/gen, consistent with the autosomal mutation rates inferred via both direct and indirect estimation approaches.

2.4 | Prevalence of Structural Variation Across the Aye-Aye Genome

Structural variants, including duplications, deletions, and inversions of at least 50 bp in size, form the largest source of heritable variation, affecting more sites than single nucleotide variants in primates (Redon et al. 2006; Conrad et al. 2010; Pang et al. 2010; Sudmant et al. 2010, 2013, Sudmant, Mallick, et al. 2015; Sudmant, Rausch, et al. 2015; Zarrei et al. 2015; Mao et al. 2024), and have the potential to impact coding and regulatory genomic regions, which can in turn have important effects on genome structure and gene expression (Chaignat et al. 2011; Chiang et al. 2017). However, due to challenges related to identification and genotyping, structural variation remains relatively poorly characterized in many species. In primates, structural variant detection has largely focused on the great apes (Mao et al. 2024) as well as biomedically relevant species (e.g., rhesus macaques; Thomas et al. 2021), with the recent study of Versoza, Jensen, et al. (2025) that characterized the landscape of structural variation in aye-ayes in fact representing the first such study in a strepsirrhine.

Utilizing high-coverage genomic data of 14 individuals, Versoza, Jensen, et al. (2025) employed an ensemble approach for identifying and genotyping structural variants from short-read data. A total of 1133 autosomal structural variants were identified, with the majority consisting of deletions (88.3%) with a median length of 172 bp. As longer deletions are likely to experience stronger purifying selection, owing to the increased likelihood of functionally altering expressed proteins, this relatively diminutive length may be expected (Taylor et al. 2004; Itsara et al. 2010; Mills et al. 2011; Y. Yang et al. 2024). Conversely, while duplications and inversions made up a smaller proportion of the identified structural variants (7.2% and 4.5%, respectively), the median length for these genomic elements together was considerably longer (424 bp). Notably, the proportions of each variant type were similar to those observed previously in humans and rhesus macaques (89.4% and 88.3% deletions, and 10.6% and 11.7% duplications, respectively; Brandler et al. 2016; Thomas et al. 2021). Of the 1133 structural variants identified in aye-ayes, 45 were predicted to exhibit major effects, with a number of these disrupting immune response genes.

3 | Direct and Indirect Estimates of Recombination Rates

In terms of evolutionary processes and outcomes, recombination is an important force that shuffles genetic variation into novel combinations and breaks up linkage blocks thereby increasing the efficacy of natural selection (Hill and Robertson 1966; Felsenstein 1974; and see the review of B. Charlesworth and Jensen 2021). The rate of recombination has been shown to vary at multiple scales, including between species, populations within species, individuals within a population, and sites within the genome (see the reviews of Ritz et al. 2017; Stapley et al. 2017). As in the case of mutation rates discussed above, it is common practice to use a species-averaged recombination rate when constructing evolutionary models, though failing to account for recombination rate heterogeneity has also been shown to result in misinference of both population history and the DFE (Soni, Pfeifer, et al. 2024; Soni and Jensen 2025; and see Dapper and Payseur 2018; Samuk and Noor 2022). Moreover, it has been well appreciated for decades that the interaction between recombination and selection is an important dictator of observed levels of local genomic variation

(Begun and Aquadro 1992; B. Charlesworth et al. 1993; and see Cutter and Payseur 2013).

3.1 | Inferring Recombination Rates From Population Genomic Data

As with mutation rate inference, approaches for inferring the recombination rate from population genomic data fall into the categories of direct and indirect approaches. Direct pedigree-based approaches involve the counting of CO (i.e., a reciprocal exchange of genetic material between homologs) and NCO (i.e., a unidirectional transfer and replacement of genetic material, with the donor left unmodified) events between the parental and offspring generations. As such, male and female recombination rates can be separately estimated. However, similar to direct pedigree-based mutation rate inference approaches, the low number of recombination events within a single generation means that there is relatively coarse resolution and a recombination rate map cannot be constructed without an exceptionally large number of pedigreed individuals (see the review of Clark et al. 2010).

To infer maps of fine-scale recombination rate heterogeneity across the genome, indirect, population-based inference approaches are commonly used. Leveraging patterns of linkage disequilibrium (LD), these approaches can infer historical patterns of recombination and therefore offer sufficient resolution to generate fine-scale recombination maps (see the reviews of Stumpf and McVean 2003; Peñalba and Wolf 2020). There are, however, a number of limitations. First, because recombination events are not directly counted from parent to offspring, sex-specific rates cannot be inferred. Second, whilst the per-generation recombination rate, r, can be estimated using direct approaches, indirect population-based approaches can only infer the population recombination rate, $\rho = 4N_e r$, where N_e is the effective population size. Thus, processes that alter patterns of genetic variation—particularly LD—can confound indirect recombination rate inference, including both population history and natural selection (Dapper and Payseur 2018; Samuk and Noor 2022). It is therefore necessary to work within the context of a fit demographic model and to mask out directly selected genomic regions as well as any linked sites (which in turn require access to an annotated genome) prior to performing recombination rate inference (Johri et al. 2020; Johri, Eyre-Walker, et al. 2022).

3.2 | Direct Pedigree-Based Estimates of CO and NCO Rates in Aye-Ayes

The rate and distribution of CO and NCO events across the genome have been shown to vary across taxonomic groups (see the reviews of Paigen and Petkov 2010; Stapley et al. 2017), and therefore estimating patterns and levels of recombination across the primate clade is key to understanding broader patterns of primate evolution. Thus far however, recombination rate estimation within primates has been focused upon the haplorrhine suborder (see Kong et al. 2002, 2010; Coop et al. 2008; Pratto et al. 2014; Williams et al. 2015; Halldorsson et al. 2016; Palsson et al. 2025 for humans; Auton et al. 2012; Stevison et al. 2016; Pfeifer and Jensen 2016 for chimpanzees; Stevison et al. 2016; Wall et al. 2022 for bonobos and gorillas; Rogers et al. 2006; Xue et al. 2016, 2020; Versoza et al. 2024 for rhesus macaques; Rogers et al. 2000; Cox et al. 2006 for baboons; Jasinska et al. 2007; Pfeifer 2020b for vervet monkeys). Recently, Versoza, Lloret-Villas, et al. (2025) provided the first direct estimation of rates of CO and NCO events in a strepsirrhine (in aye-ayes). The authors tracked recombination events across 6 three-generation pedigrees and 3 two-generation nuclear families, identifying 305 (163 maternal and 142 paternal) CO and 200 (95 maternal and 105 paternal) NCO events across the aye-aye autosomes, yielding a genome-wide, sex-averaged CO rate of 0.85 cM/Mb (0.77 and 0.94 cM/Mb in males and females, respectively) and a sex-averaged NCO rate of 6.8×10^{-7}/bp/gen (95% CI: 2.9×10^{-7} to 1.1×10^{-6}/bp/gen). The estimated CO rate is considerably lower than the rate estimated in humans by Bhérer et al. (2017) of 1.3 and 2.0 cM/Mb in males and females, respectively. This reduced recombination rate may partially explain the lower levels of genetic diversity observed in aye-ayes relative to other primates (Figure 2a; Perry et al. 2013; Terbot, Soni, Versoza, Pfeifer, et al. 2025). However, the parental age effect observed in humans (Porubsky et al. 2025) and chimpanzees (Venn et al. 2014), whereby the number of CO events decreases with parental age, was also observed in aye-ayes (Figure 2b). Furthermore, the sex-averaged mean NCO tract length was similar to those observed in other primates (Jeffreys and May 2004; Palsson et al. 2025 for humans; Wall et al. 2022 for baboons; Versoza et al. 2024 for rhesus macaques)—see Figure 2c for a comparison with humans. Finally, Versoza, Lloret-Villas, et al. (2025) identified a putative sequence motif of a PRDM9 binding site in aye-ayes that bore similarities to the human PRDM9 binding motifs identified by Altemose et al. (2017).

3.3 | Indirect Polymorphism-Based Estimates of the Fine-Scale Recombination Rate in Aye-Ayes

The first maps of fine-scale recombination rates in aye-ayes (and again the first in a strepsirrhine species) were inferred by Soni, Versoza, Terbot, et al. (2025), utilizing the LD-based, demography-aware recombination rate estimator pyrho (Spence and Song 2019). It has previously been shown that pyrho underestimates the population-scaled recombination rate when a population has undergone a recent decline, particularly when the sample size is small (Dutheil 2024). Given that the Soni, Versoza, Terbot, et al. (2025) study sampled five individuals, and that the demographic model inferred in aye-ayes by Terbot, Soni, Versoza, Pfeifer, et al. (2025) suggested a population bottleneck followed by an extremely recent population decline (see Section 4), an underestimate of the population-scaled recombination rate would thus be expected, as confirmed by benchmarking performed by the authors under this demographic model. To account for this underestimation, the authors performed recombination rate estimation using pyrho under the Terbot, Soni, Versoza, Pfeifer, et al. (2025) aye-aye demographic model and rescaled the estimated recombination rates such that the total inferred genetic map length was equal to the length observed in the pedigree-based study of Versoza, Lloret-Villas, et al. (2025). This rescaling procedure maintained the inferred variation in recombination rates across the aye-aye genome, which found elevated recombination rates near the telomeric

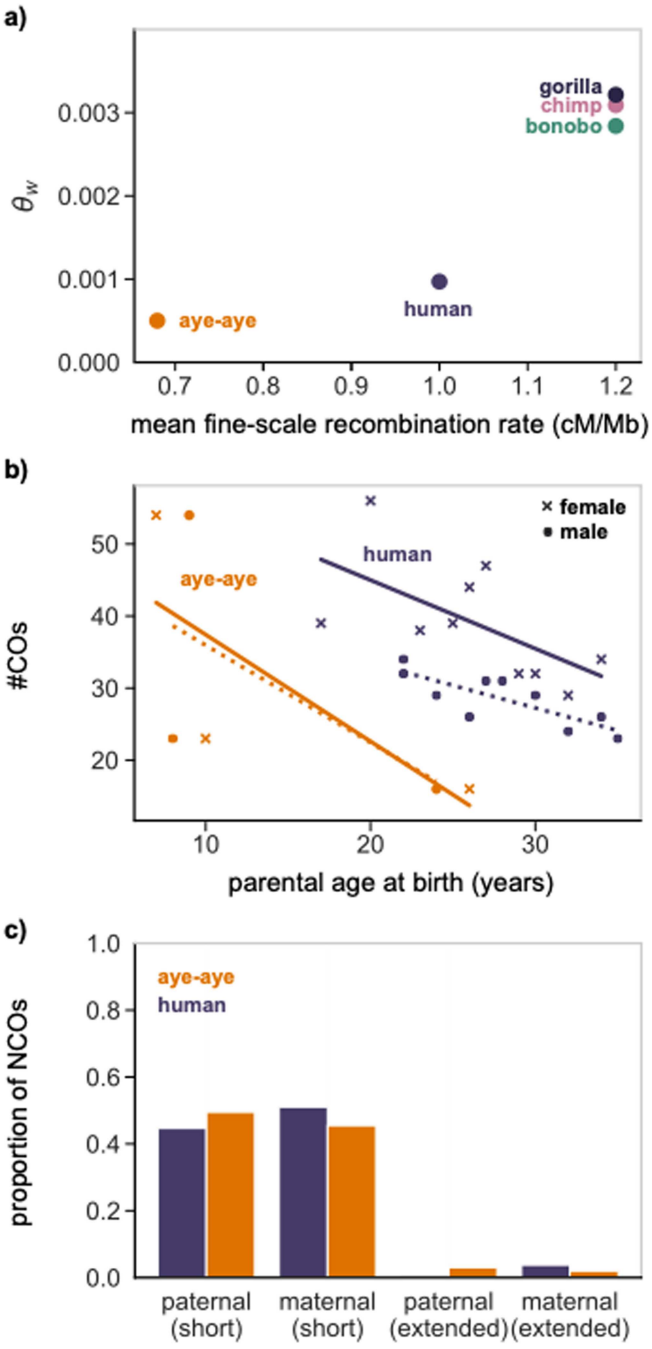

FIGURE 2 | (a) Levels of genetic variation (as represented by θ_w) plotted against pedigree-based recombination rates. Pedigree-based recombination rates were obtained from Kong et al. (2002) for humans; Stevison et al. (2016) for bonobos, chimpanzees, and gorillas; and Soni, Versoza, Terbot, et al. (2025) for aye-ayes. (b) Number of CO events plotted against parental age at birth in humans (Williams et al. 2015) and aye-ayes (Versoza, Lloret-Villas, et al. 2025). Solid linear regression lines represent females, dotted lines represent males. (c) Distribution of NCO tract lengths in humans (Palsson et al. 2025) and aye-ayes (Versoza, Lloret-Villas, et al. 2025). Short tract lengths are those that are < 1 kb in length, whilst extended are > 1 kb.

ends, and reduced rates within centromeric and pericentromic regions—a pattern of heterogeneity that has also been observed in other primates (Auton et al. 2012; Stevison et al. 2016; Pfeifer 2020a; Wall et al. 2022; Versoza et al. 2024; Soni, Versoza, Jensen, et al. 2025; Terbot, Calahorra-Oliart, et al. 2025). The mean rescaled genome-wide recombination rate was 0.68 cM/Mb, which is notably lower than previous estimates in haplorrhines (~1 cM/Mb for humans [Kong et al. 2002] and ~1.2 cM/Mb for bonobos, chimpanzees, and gorillas [Stevison et al. 2016]).

Finally, in primates, one would expect lower levels of recombination on sex chromosomes relative to autosomes, owing both to the lower N_e in the former as well as to the absence of recombination in the non-pseudoautosomal region (non-PAR) whilst in males (Singh et al. 2007; D. Charlesworth 2017; Olito and Abbott 2025). In agreement with these expectations, Terbot, Soni, Versoza, Milhaven, et al. (2025) found that the population-scaled recombination rate on the aye-aye X chromosome was roughly 70% lower than the autosomal rate inferred by Soni, Versoza, Terbot, et al. (2025).

4 | Inference of Historical Population Size Change and Structure

As an important determinant of genetic variation, genetic drift is a fundamental evolutionary process. Per-generation genetic drift effects are stronger in smaller populations, with larger expected stochastic fluctuations in allele frequencies from one generation to the next. Though levels and patterns of genetic variation were once assumed to be primarily shaped by selective forces such as purifying and balancing selection (see Crow 1987 and Lewontin 1987 for details of the *classical/balanced* debate), *The Neutral Theory of Molecular Evolution* argued that observed variation and divergence were likely largely explained by genetic drift alone (Kimura 1968, 1983). Subsequent empirical analysis has generally confirmed Kimura's view (see the commentary of Jensen et al. 2019). Moreover, in primate genomes specifically, our improved understanding of genome architecture since Kimura's initial proposal has demonstrated the great majority of the genome to be nonfunctional and thus neutrally evolving. Inferring a well-fitting demographic model, including details of population size change, population structure, and gene flow between populations, is therefore an important aspect of population genetic inference in explaining genome-wide patterns of variation.

A central challenge when performing demographic inference is disentangling the relative roles of both neutral and selective processes in shaping variation. Failure to do so can result in misinference of the demographic model itself and/or of underlying model parameters. For instance, BGS (B. Charlesworth et al. 1993) and recurrent selective sweeps (Maynard Smith and Haigh 1974) can both result in a skew in the site frequency spectrum (SFS) toward rare alleles, which is also characteristic of neutral population growth (Kim 2006; Jensen et al. 2007; Nicolaisen and Desai 2012, 2013; Ewing and Jensen 2016; Johri et al. 2021; Soni et al. 2023; and see the reviews of B. Charlesworth and Jensen 2021, 2024), with the effects of these processes further modified by the underlying variation in mutation and recombination rates across the genome (Dapper and Payseur 2018; Samuk and Noor 2022; Soni, Pfeifer, et al. 2024).

An important first question when performing demographic inference is thus how one might account for the biasing effects of natural selection, with the primary concern being the effects

generated by the dominant action of purifying selection and BGS in and around functional genomic elements. The most appropriate approach will depend on the genomic architecture of the species in question. For example, species with coding-dense genomes (meaning genomes composed of a large proportion of functional regions that are experiencing direct selection) may have few or no genomic regions unaffected either directly by selection, or by the effects of selection at linked sites (e.g., Irwin et al. 2016; Sackman et al. 2019; Jensen 2021; Morales-Arce et al. 2022; Terbot, Johri, et al. 2023; Terbot, Cooper, et al. 2023; Howell et al. 2023; Soni, Terbot, Jensen 2024). In such cases, selection must be directly and simultaneously modeled along with population history. For example, Johri et al. (2020, 2023) developed an approximate Bayesian computation approach for joint inference of demography and the DFE. This approach utilizes information from multiple aspects of the data, including the SFS, LD, and divergence. However, because of the need to jointly infer the parameters of demography and selection, this approach has been limited thus far to inferring relatively simple demographic models, in which a single step-size change in population size is fit to the data.

In species with coding-sparse genomes however (i.e., in which a large proportion of the genome is nonfunctional), such as that characterizing primates as mentioned above, demographic and selection inference can be performed separately in a step-wise approach. Such "two-step" inference approaches (see Soni and Jensen 2025; Soni, Versoza, Vallender, et al. 2025; Soni et al. 2025a) involve first performing demographic inference on neutral intergenic regions that are at a sufficient recombinational distance from functional sites such that they are not subject to BGS effects (B. Charlesworth et al. 1993), followed by the inference of selective processes on functional sites in the second step conditional on the inferred demographic history. Because these processes are separately inferred, neutral demographic estimators (e.g., Gutenkunst et al. 2009; Excoffier et al. 2013) can be utilized to infer more parameter-rich demographic models, though mutation and recombination rate heterogeneity must also be carefully modeled.

4.1 | Inferring the Population History of Aye-Ayes From Population Genomic Data

Perry et al. (2013) provided the first genetic insights into the population history of aye-ayes, primarily focusing on population structuring. The authors generated low-coverage (7.1–10.6×) sequencing data from 12 aye-ayes sampled from across the North ($n = 4$), West ($n = 3$), and East ($n = 5$) regions of Madagascar. Calculating single nucleotide polymorphism (SNP) distances from their estimated neighbor-joining tree, Perry et al. (2013) found that the East and West populations were more similar to one another than to the North population. This pattern was consistent when limiting analysis to synonymous sites only. Consistent with previous studies (Perry, Melsted, et al. 2012; Perry, Reeves, et al. 2012), the authors also found that aye-ayes exhibit the lowest levels of genetic diversity of any studied primate species to date.

More recently, Terbot, Soni, Versoza, Pfeifer, et al. (2025) inferred the population history of aye-ayes based on a combined data set of the low-coverage data for the 12 individuals sequenced by Perry et al. (2013), together with new high-coverage (> 50×) sequence data obtained from five individuals housed at the Duke Lemur Center (either wild-born or from wild-born parents). The authors called variants from sequence reads mapped to the high-quality, fully annotated, chromosome-level aye-aye assembly of Versoza and Pfeifer (2024). Importantly, this reference enabled the masking of sites likely impacted by purifying and background selection, given the inference concerns discussed above (e.g., Ewing and Jensen 2014, 2016; Johri et al. 2020, 2021; and see the reviews of B. Charlesworth and Jensen 2021, 2024). More specifically, the authors masked functional regions, and 10 kb flanking each functional region, which is a likely sufficient recombinational distance to avoid the strongest BGS effects in primate genomes (see Johri et al. 2020 for an analytical approach to calculating sufficient distances).

As identifying the number of populations in a data set is an important first step when performing demographic inference, in that it limits the number of candidate demographic models on which to perform inference, this was first investigated. In agreement with Perry et al. (2013), Terbot, Soni, Versoza, Pfeifer, et al. (2025) found that two populations best explained the population in their combined data set, putatively titled the North and non-North populations. Working from this two-population model, Terbot, Soni, Versoza, Pfeifer, et al. (2025) then inferred well-fitting population histories using two widely applied neutral SFS-based estimators, fastsimcoal2 (the coalescent-based approach of Excoffier et al. 2013) and *δaδi* (the diffusion approximation-based approach of Gutenkunst et al. 2009). Reassuringly, both approaches inferred similar best-fitting models in terms of the underlying population sizes and timing of population size change. The fit of these models was further verified by simulating the best-fitting models for direct comparison to the empirically observed SFS, and a strong correspondence was observed between simulated and observed, with the fastsimcoal2 model providing the best fit (Figure 3). This model inferred an ancestral population of size ~11,750 individuals that split into 2 daughter populations, together with experiencing a population bottleneck 1133 generations ago. These North and non-North daughter populations were of size 1410 and 3453 individuals, respectively, at the time of the split, though both underwent a further recent decline in size, beginning 7 generations ago. Taken together, this model resulted in a current-day North population size of 262 individuals and a non-North population size of 642 individuals.

Notably, this model corresponds well to the history of Madagascar itself. Louis et al. (2020) estimated an aye-aye generation time of 5 years, suggesting that the population bottleneck at the time of the population split occurred roughly 5500 years ago, which coincides with the estimated time of human arrival to Madagascar (Dewar and Richard 2012; Salmona et al. 2017; Hansford et al. 2020; Balboa et al. 2024). The timing of the more recent population decline, which was estimated to have begun ~35 years ago, falls within the 20–40 year range in which aye-aye populations have been observed to have experienced a further ~50% reduction in population size owing largely to habitat destruction (Louis et al. 2020). Whilst this well-fitting demographic model facilitates further population genetic inference in aye-ayes (see Section 5), it also draws attention to

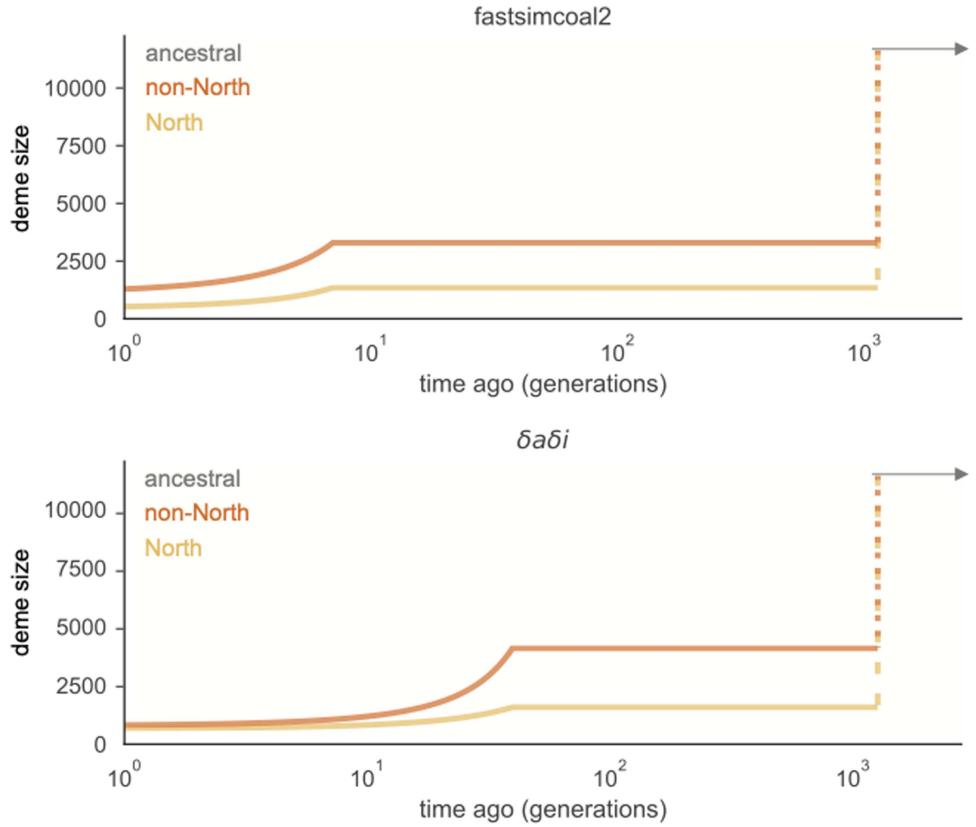

FIGURE 3 | Best-fitting demographic models for aye-aye population history as inferred by fastsimcoal2 (top) and *δaδi* (bottom) by Terbot, Soni, Versoza, Pfeifer et al. (2025). *X*-axes are scaled in log generations.

the current critical juncture in which this rapid and ongoing decline in aye-aye populations has resulted in an effective size likely below 2000 individuals.

4.2 | Comparing the Autosomal and X Chromosomal Population Histories of Aye-Ayes

The evolutionary history of sex chromosomes can deviate from that of the autosomes due to a myriad of factors including the population sex ratio as well as sex-biased migration (Bachtrog et al. 2009; and see the reviews of Ellegren 2011 and Bachtrog et al. 2014 for a detailed discussion of factors). Furthermore, the ratio of N_e on the X chromosome relative to the autosomes in primates is expected to be 3:4 (though this may vary depending on the mating system), with this factor alone leading to an expectation of a 25% reduction in genetic variation on the X. Deviations from this expected diversity have been observed in humans (e.g., Keinan et al. 2009) as well as in gorillas and orangutans (Prado-Martinez et al. 2013). Given the aye-ayes' endangered status and nocturnal lifestyle, comparing genomic patterns observed in the X chromosome to those of the autosomes therefore provides an opportunity to estimate these otherwise difficult to observe sex ratios.

By first identifying the pseudoautosomal boundary in aye-ayes, Terbot, Soni, Versoza, Milhaven, et al. (2025) studied the evolutionary dynamics of the non-PAR in the 12 non-North individuals described in Terbot, Soni, Versoza, Pfeifer, et al. (2025). Simulating under the demographic model inferred in that study (with a rescaled mutation rate of 2.22×10^{-8} /bp/gen, in order to account for the differing male and female mutation rates inferred by Versoza, Ehmke, et al. 2025), the authors found that the autosomal model indeed fit the empirical non-PAR data well after rescaling, and therefore the inferred population history was consistent across both autosomes and the X chromosome. Furthermore, a 1:1 male-to-female sex ratio was found to be most consistent with the observed data, despite the ecological and territorial range differences (with male ranges thought to be ~50 times larger than those of females).

5 | Inference of Selective Dynamics

The inference of natural selection from population genomic data consists of both the characterization of commonly acting selective dynamics as captured by the DFE (e.g., purifying selection) as well as recent, comparatively rare episodic selective dynamics such as the selective sweep effect potentially generated by positive selection. The DFE describes the spectrum of mutational selection coefficients, and a DFE may thus be described that characterizes all newly arising mutations, only segregating variation, or only fixations. Because it is largely a description of selective constraint—that is, there are far more deleterious mutations occurring than beneficial mutations—the DFE is expected to remain relatively stable over long evolutionary timescales. By quantifying the relative proportion of neutral, weakly deleterious, and strongly deleterious mutations, as well as the fraction of beneficial variants, the DFE thus describes general selective dynamics in functional regions of the genome (see the reviews of Eyre-Walker and Keightley 2007;

Keightley and Eyre-Walker 2010; Bank et al. 2014), and as such is essential for developing a population-specific evolutionary baseline model from which to perform downstream inference (Comeron 2014, 2017; Johri, Aquadro, et al. 2022; Soni and Jensen 2025).

The DFE can be modeled as a continuous or discrete distribution of mutational selection coefficients. Two main approaches have been developed for inferring the DFE from polymorphism and/or divergence data. The most commonly used is the two-step SFS-based approach (see Keightley and Eyre-Walker 2010). First, a demographic model is inferred from the SFS of synonymous sites, then in Step 2, a DFE is fit to the nonsynonymous SFS, conditional on the demographic model inferred in Step 1 (Eyre-Walker and Keightley 2007, 2009; Boyko et al. 2008; Schneider et al. 2011; Galtier 2016; Tataru et al. 2017). Hence, a crucial assumption of these approaches is that synonymous sites are evolving neutrally, though there is indeed considerable evidence that this may not be the case in many organisms (e.g., Chamary and Hurst 2005). In addition, BGS effects generated from direct selection on neighboring nonsynonymous variants are likely to skew the SFS of synonymous sites, and Johri et al. (2021) demonstrated that neglecting to account for these BGS effects can lead to demographic misinference. Furthermore, Soni, Pfeifer, et al. (2024) found that assuming a single mutation and recombination rate (i.e., neglecting to account for mutation and recombination rate heterogeneity across the genome), as is common practice, can also result in misinference of the DFE. In order to address some of these inference difficulties, Johri et al. (2020) developed an approximate Bayesian computation approach for jointly inferring demography and the DFE, thereby accounting for the biasing effects of selection on demographic inference and demography on DFE inference, whilst also modeling fine-scale mutation and recombination heterogeneity.

Whilst the DFE largely models constantly operating selective processes, selective sweeps and balancing selection are relatively ephemeral on evolutionary timescales. These processes leave differing genomic signatures in terms of patterns of local variation. The time that it takes for a beneficial mutation to reach fixation, and the size of the genomic neighborhood that is affected by the resulting selective sweep effect, are dependent on the strength of selection and the local recombination rate. The characteristic signatures of a selective sweep include a local reduction in nucleotide diversity (Berry et al. 1991) and a localized skew in the SFS toward both low and high frequency derived alleles (Braverman et al. 1995; Simonsen et al. 1995). The theoretical expectations of these dynamics under a model of a single, recent selective sweep form the basis of the composite likelihood ratio (CLR) test of Kim and Stephan (2002). Many commonly used methods for performing genome scans for recent positive selection are based on this original CLR framework (e.g., SweepFinder and its successor SweepFinder2; Nielsen et al. 2005; DeGiorgio et al. 2016). These implementations utilize the empirically observed SFS as a null model, thereby partially accounting for underlying demographic processes that can impact inference and result in an excess of false positives (e.g., Jensen et al. 2005; B. Charlesworth and Jensen 2022).

Though balancing selection may also be considered an episodic process, a mutation can be maintained under balancing selection across much greater timescales. Fijarczyk and Babik (2015) characterized recent balancing selection as that in which the balanced mutation has been segregating for $< 0.4N_e$ generations, whilst at the other extreme, ancient balancing selection has been acting for $> 4N_e$ generations. Furthermore, whilst selective sweeps reduce variation in their genomic neighborhood, balancing selection maintains variation that has accrued on the balanced haplotype (see the reviews of Fijarczyk and Babik 2015; Bitarello et al. 2023). This maintenance of variation at intermediate frequencies results in a local skew in the SFS toward intermediate frequency alleles; as such, the inference of balancing selection can be confounded by both population history and other forms of selection that replicate these patterns. Soni and Jensen (2024) demonstrated via simulation that the initial trajectory of a beneficial mutation is identical whether its ultimate fate is that of a hard selective sweep or to be maintained under balancing selection, whilst population contraction (Soni and Jensen 2024) and population structure (Lewontin and Krakauer 1973; B. Charlesworth et al. 2003; de Filippo et al. 2016; and see the review of Bitarello et al. 2023) have both been shown to potentially replicate these patterns neutrally, again necessitating a careful consideration of population history when performing such genomic scans.

5.1 | Inferring the DFE in Aye-Ayes From Population Genomic Data

Utilizing the 447-way multiple species alignment (Zoonomia Consortium 2020; Kuderna et al. 2023), updated by Soni, Versoza, Terbot, et al. (2025) to include the high-quality annotated aye-aye genome of Versoza and Pfeifer (2024; see Section 2.3 for further details), Soni et al. (2025b) estimated levels of exonic divergence in aye-ayes. Consistent with expectations of the action of purifying selection in functional regions, mean genome-wide exonic divergence was found to be lower than mean neutral divergence. On an individual gene basis, Soni et al. (2025b) also quantified genes with high levels of divergence as candidates for long-term positive selection, though notably relaxed selective constraint can also generate these patterns. Via gene function analysis, the authors identified sensory-related and immune-related functions to be rapidly evolving. Given that aye-ayes are nocturnal, with dichromatic vision aiding moonlight foraging (Perry et al. 2007), and scent used both to attract mates (Winn 1994) and to identify one another (Price and Feistner 1994), rapid evolution of sensory-related genes is consistent with aye-aye behavior, physiology, and morphology. Meanwhile, high evolutionary rates in immune-related genes have been observed across many vertebrate species, as they engage in an evolutionary arms race with various pathogens (e.g., George et al. 2011; Rausell and Telenti 2014).

Although the DFE can be inferred from polymorphism data alone, divergence is important for capturing long-term patterns of selection. Thus, Soni et al. (2025b) used a combination of exonic divergence data together with polymorphism data in order to infer a well-fitting discrete DFE consisting of effectively neutral and weakly deleterious ($2N_{ancestral}s < 10$, where $N_{ancestral}$ is the ancestral aye-aye population size inferred by Terbot, Soni, Versoza, Pfeifer, et al. 2025, and s is the reduction in fitness of the mutant homozygote relative to the wildtype), moderately deleterious ($10 \leq 2N_{ancestral}s < 100$), and strongly deleterious ($100 \leq 2N_{ancestral}s < 1000$) mutational classes in aye-ayes. Specifically, they simulated a 54.9-million-year divergence time (Horvath et al. 2008), followed by the Terbot, Soni, Versoza, Pfeifer, et al. (2025) aye-aye demographic model, performing a

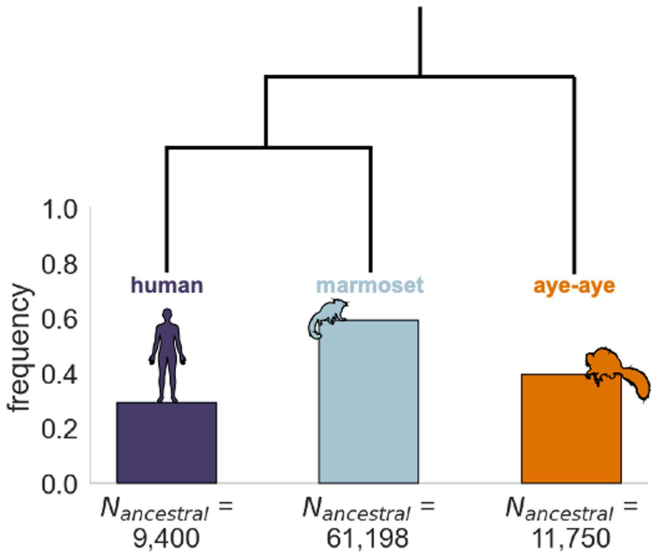

FIGURE 4 | Proportion of moderately and strongly deleterious exonic mutations (i.e., mutations experiencing a population-scaled strength of selection $2N_{ancestral}s > 10$, where $N_{ancestral}$ is the ancestral population size, and s is the reduction in fitness of the mutant homozygote relative to the wildtype) for humans (*Homo sapiens*), the common marmoset (*Callithrix jacchus*) and aye-ayes (*Daubentonia madagascariensis*). $N_{ancestral}$ values were obtained from inferred demographic models for humans (Soni and Jensen 2025), common marmosets (Soni, Versoza, Vallender, et al. 2025), and aye-ayes (Terbot, Soni, Versoza, Pfeifer, et al. 2025), whilst the proportion of moderately and strongly deleterious mutations were obtained from DFEs inferred in humans (Johri et al. 2023), common marmosets (Soni et al. 2025a), and aye-ayes (Soni et al. 2025b).

grid search of DFE parameters to fit simulated divergence to the observed levels of exonic divergence. The best-fitting DFE is characterized by 60% of mutations being effectively neutral or weakly deleterious, 20% moderately deleterious, and 20% strongly deleterious. The inferred proportion of moderately and strongly deleterious mutations (i.e., $2N_{ancestral}s > 10$) is depicted in Figure 4, along with the proportions from the DFEs inferred for humans by Johri et al. (2023) and for common marmosets by Soni et al. (2025a) for comparison. Although DFE inference has been performed in numerous other primates (e.g., Castellano et al. 2019), these examples presented here utilize common inference approaches and are therefore readily comparable. Notably, the proportion of moderately and strongly deleterious mutations scales with $N_{ancestral}$ across the three species, with humans having the lowest ancestral population size and proportion of moderately and strongly deleterious mutations, and common marmosets having the highest. This is consistent with the theoretical expectation of stronger selective effects in species with larger N_e.

5.2 | Targets of Recent Positive Selection and Balancing Selection in Aye-Ayes

For more episodic forms of selection such as selective sweeps and balancing selection, it is common to scan the genome for localized signatures of selection in a given genomic window. Soni, Terbot, Versoza, et al. (2025) performed whole-genome scans in aye-ayes on a data set of five unrelated individuals sequenced to high-coverage (> 50×). Though outlier approaches are popular for identifying selection candidates, such approaches are not only associated with high false positive rates (Teshima et al. 2006; Thornton and Jensen 2007), but also rely on an arbitrary choice of outlier threshold (often 1% or 5%). As any evolutionary model will result in a distribution of variation, and as it is not a given that selected loci will reside in the tails of the distribution under a given demographic history, these outlier approaches are unsatisfactory (see Harris et al. 2018; Jensen 2023). Instead, Soni, Terbot, Versoza, et al. (2025) simulated each full-length aye-aye autosome 10 times under the inferred evolutionarily baseline model (Johri, Aquadro, et al. 2022), utilizing the Terbot, Soni, Versoza, Pfeifer, et al. (2025) aye-aye population history, and performed inference for selective sweeps and balancing selection. The maximum CLR value across these simulations was set as the null threshold for empirical inference, under the logic that this represents the highest value that can be generated in the absence of positive or balancing selection. As such, any region in excess of that value in the empirical data is a selection candidate (see Soni et al. 2023).

Having generated null thresholds, Soni, Terbot, Versoza, et al. (2025) identified 3462 recent positive selection candidates using SweepFinder2 (DeGiorgio et al. 2016), with inference performed at each SNP, mapping onto 71 genes. Scans for balancing selection using the B_{0MAF} approach of Cheng and DeGiorgio (2020), with inference performed across 100 SNP windows, yielded 163 candidate windows mapping to 60 candidate genes. A gene functional analysis on selective sweep candidate genes yielded no gene ontology (GO) terms that passed both the p value and false discovery rate thresholds of 0.05. However, 14 GO terms from the balancing selection candidate genes met both thresholds. Figure 5a,b depicts the results of these genome scans. Seven of the 14 GO terms were related to olfaction, with a > 5-fold enrichment. Furthermore, several olfactory receptor genes were candidates for balancing selection. As discussed above, aye-ayes use scent-marking behaviors when attracting mates (Winn 1994) and discriminate based on scent (Price and Feistner 1994). It is therefore interesting to note that these recent studies in aye-ayes have identified genes related to olfaction as evolving rapidly over evolutionary timescales, and as also being maintained by balancing selection. Six functions related to G protein-coupled receptors (GPCRs) were also implicated as experiencing balancing selection by Soni, Terbot, Versoza, et al. (2025), with a ≥ 3.75-fold enrichment. GPCRs are involved in multiple physiological processes and are responsible for activating cellular responses when extracellular molecules are detected. They are thus important in terms of how aye-ayes interact with their environment. Two of these GPCR-related functions were related to the opsin responsible for mediating dim light vision, rhodopsin (Litman and Mitchell 1996), again suggesting that functions with a rapid long-term evolutionary rate have also been implicated as experiencing balancing selection in aye-ayes. Figure 5c provides the proportion of significant, enriched gene function categories that are related to olfaction and vision. Finally, genes from the PATE family were identified as candidates for both recent positive and balancing selection. These genes are thought to be involved in sperm maturation (Soler-García et al. 2005) and sperm–oolemma fusion (Margalit et al. 2012). As multiple primate species have

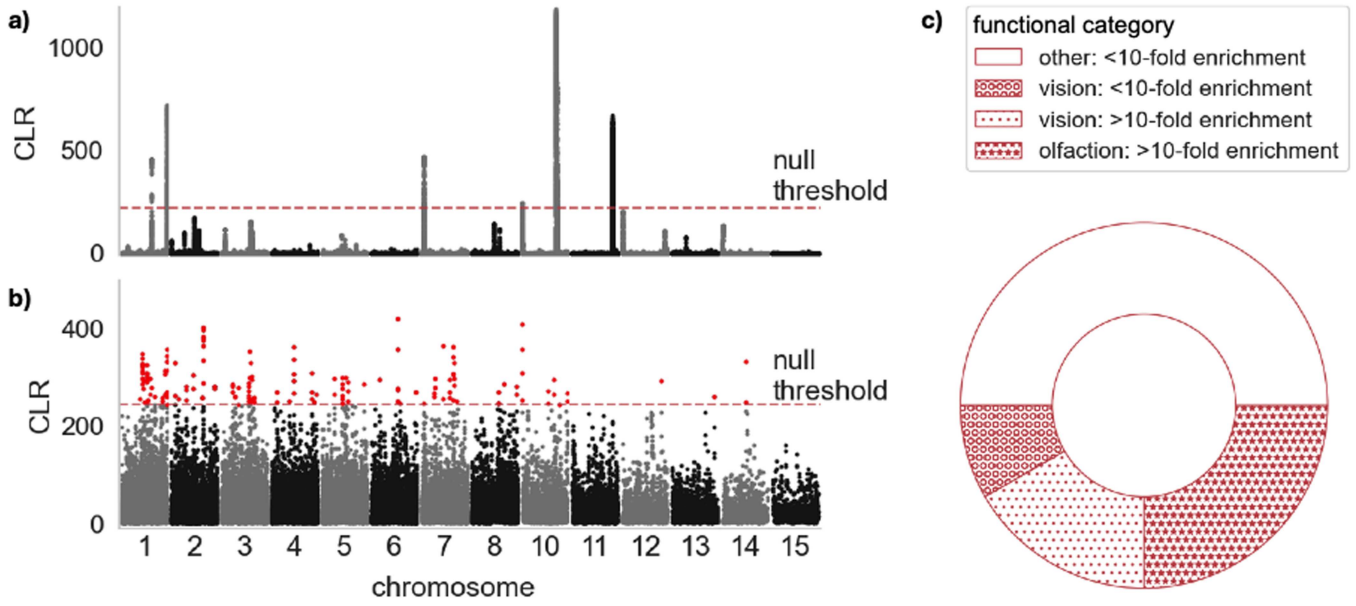

FIGURE 5 | (a) Genomic scans for selective sweeps across aye-aye autosomes. (b) Genomic scans for balancing selection across aye-aye autosomes. Candidate loci are marked in red to indicate their contribution to enriched functional categories. (c) Pie chart showing the number of enriched gene function categories. Data from Soni, Terbot, Versoza, et al. (2025).

been shown to use coagulated ejaculate to prevent sperm competition by blocking out sperm from rival males, particularly in polygynandrous species such as aye-ayes (Dixson et al. 2005; Quinn and Wilson 2004; Martinez and Garcia 2020), it may be hypothesized that sexual selection is shaping the PATE family of genes.

Finally, Terbot, Soni, Versoza, Milhaven, et al. (2025) followed the approach of Soni, Terbot, Versoza, et al. (2025) in order to identify patterns of exonic divergence and perform genomic scans for recent positive selection and balancing selection on the aye-aye X chromosome. However, the authors found no evidence of rapidly evolving exonic regions on this sex chromosome. This result implies that, if positive or balancing selection are operating on this chromosome, these processes are not detectable within the context of the X chromosome baseline model (Poh et al. 2014; Johri, Eyre-Walker, et al. 2022; Jensen 2023).

6 | Concluding Thoughts

Although the first aye-aye reference genome was published over a decade ago (Perry, Reeves, et al. 2012), it was only with the publication of the chromosome-level reference genome with gene annotations of Versoza and Pfeifer (2024), and the generation of novel high-coverage population genomic data, that in-depth population genetic modeling of the evolutionary processes shaping variation in aye-ayes became feasible. The variety of analyses summarized here has well elucidated the general population genetic environment shaping levels and patterns of variation and divergence in this species, including its underlying population history, as well as mutation rates, crossover and noncrossover rates, and purifying selection effects. Utilizing the baseline model characterized by these constantly operating processes, further studies have additionally characterized the episodic effects of positive and balancing selection, identifying in particular genes implicated in both olfaction and vision.

Taken together, these findings also highlight the precarious situation of aye-ayes in the wild, with low levels of variation shaped by both a population decline upon initial human contact on Madagascar, as well as a recent severe decline likely driven by persistent deforestation (Suzzi-Simmons 2023; Terbot, Soni, Versoza, Pfeifer, et al. 2025), together with amongst the lowest mutation rates observed in primates (Soni, Versoza, Terbot et al. 2025; Versoza, Ehmke, et al. 2025) and relatively low sex-averaged recombination rates (Versoza, Lloret-Villas, et al. 2025). Furthermore, the characterization of long-term and episodic selection dynamics has shed some light on the potentially changing selection pressures that aye-ayes are facing with ongoing habitat destruction. These recent, novel insights into the landscape of evolutionary processes in aye-ayes thus represent a valuable resource for future conservation management strategies, as well as for virtually any primate comparative genomics given the unique position of aye-ayes in the primate clade.

Acknowledgments

This work was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Numbers R35GM151008 to S.P.P. and R35GM139383 to J.D.J. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

References

Agarwal, I., and M. Przeworski. 2019. "Signatures of Replication Timing, Recombination, and Sex in the Spectrum of Rare Variants on the

Human X Chromosome and Autosomes." *Proceedings of the National Academy of Sciences of the United States of America* 116: 17916–17924. https://doi.org/10.1073/pnas.1900714116.

Altemose, N., N. Noor, E. Bitoun, et al. 2017. "A Map of Human PRDM9 Binding Provides Evidence for Novel Behaviors of PRDM9 and Other Zinc-Finger Proteins in Meiosis." *eLife* 6: e28383. https://doi.org/10.7554/eLife.28383.

Auton, A., A. Fledel-Alon, S. Pfeifer, et al. 2012. "A Fine-Scale Chimpanzee Genetic Map From Population Sequencing." *Science* 336: 193–198. https://doi.org/10.1126/science.1216872.

Bachtrog, D., J. D. Jensen, and Z. Zhang. 2009. "Accelerated Adaptive Evolution on a Newly Formed X Chromosome." *PLoS Biology* 7, no. 4: e1000082. https://doi.org/10.1371/journal/pbio.1000082.

Bachtrog, D., J. E. Mank, C. L. Peichel, et al. 2014. "Sex Determination: Why so Many Ways of Doing It." *PLoS Biology* 12: e1001899. https://doi.org/10.1371/journal.pbio.1001899.

Baer, C. F., M. M. Miyamoto, and D. R. Denver. 2007. "Mutation Rate Variation in Multicellular Eukaryotes: Causes and Consequences." *Nature Reviews Genetics* 8: 619–631. https://doi.org/10.1038/nrg2158.

Balboa, R. F., L. D. Bertola, A. Brüniche-Olsen, et al. 2024. "African Bushpigs Exhibit Porous Species Boundaries and Appeared in Madagascar Concurrently With Human Arrival." *Nature Communications* 15: 172. https://doi.org/10.1038/s41467-023-44105-1.

Bank, C., G. B. Ewing, A. Ferrer-Admettla, M. Foll, and J. D. Jensen. 2014. "Thinking Too Positive? Revisiting Current Methods of Population Genetic Selection Inference." *Trends in Genetics* 30, no. 12: 540–546. https://doi.org/10.1016/j.tig.2014.09.010.

Begun, D. J., and C. F. Aquadro. 1992. "Levels of Naturally Occurring DNA Polymorphism Correlate With Recombination Rates in *D. melanogaster*." *Nature* 356: 519–520. https://doi.org/10.1038/356519a0.

Benadi, G., C. Fichtel, and P. Kappeler. 2008. "Intergroup Relations and Home Range Use in Verreaux's Sifaka (*Propithecus verreauxi*)." *American Journal of Primatology* 70: 956–965. https://doi.org/10.1002/ajp.20588.

Bergeron, L. A., S. Besenbacher, J. Bakker, et al. 2021. "The Germline Mutational Process in Rhesus Macaque and Its Implications for Phylogenetic Dating." *GigaScience* 10, no. 5: giab029. https://doi.org/10.1093/gigascience/giab029.

Bergeron, L. A., S. Besenbacher, J. Zheng, et al. 2023. "Evolution of the Germline Mutation Rate Across Vertebrates." *Nature* 615, no. 7951: 285–291. https://doi.org/10.1038/s41586-023-05752-y.

Berry, A. J., J. W. Ajioka, and M. Kreitman. 1991. "Lack of Polymorphism on the *Drosophila* Fourth Chromosome Resulting From Selection." *Genetics* 129: 1111–1117. https://doi.org/10.1093/genetics/129.4.1111.

Besenbacher, S., C. Hvilsom, T. Marques-Bonet, T. Mailund, and M. H. Schierup. 2019. "Direct Estimation of Mutations in Great Apes Reconciles Phylogenetic Dating." *Nature Ecology & Evolution* 3, no. 2: 286–292. https://doi.org/10.1038/s41559-018-0778-x.

Besenbacher, S., P. Sulem, A. Helgason, et al. 2016. "Multi-Nucleotide *De Novo* Mutations in Humans." *PLoS Genetics* 12, no. 11: e1006315. https://doi.org/10.1371/journal.pgen.1006315.

Bhérer, C., C. L. Campbell, and A. Auton. 2017. "Refined Genetic Maps Reveal Sexual Dimorphism in Human Meiotic Recombination at Multiple Scales." *Nature Communications* 8, no. 1: 14994. https://doi.org/10.1038/ncomms14994.

Bitarello, B. D., D. Y. C. Brandt, D. Meyer, and A. M. Andrés. 2023. "Inferring Balancing Selection From Genome-Scale Data." *Genome Biology and Evolution* 15: evad032. https://doi.org/10.1093/gbe/evad032.

Boyko, A. R., S. H. Williamson, A. R. Indap, et al. 2008. "Assessing the Evolutionary Impact of Amino Acid Mutations in the Human Genome." *PLoS Genetics* 4: e1000083. https://doi.org/10.1371/journal.pgen.1000083.

Brandler, W. M., D. Antaki, M. Gujral, et al. 2016. "Frequency and Complexity of *De Novo* Structural Mutation in Autism." *American Journal of Human Genetics* 98, no. 4: 667–679. https://doi.org/10.1016/j.ajhg.2016.02.018.

Braverman, J. M., R. R. Hudson, N. L. Kaplan, C. H. Langley, and W. Stephan. 1995. "The Hitchhiking Effect on the Site Frequency Spectrum of DNA Polymorphisms." *Genetics* 140: 783–796. https://doi.org/10.1093/genetics/140.2.783.

Campbell, C. D., J. X. Chong, M. Malig, et al. 2012. "Estimating the Human Mutation Rate Using Autozygosity in a Founder Population." *Nature Genetics* 44, no. 11: 1277–1281. https://doi.org/10.1038/ng.2418.

Campbell, C. R., G. P. Tiley, J. W. Poelstra, et al. 2021. "Pedigree-Based and Phylogenetic Methods Support Surprising Patterns of Mutation Rate and Spectrum in the Gray Mouse Lemur." *Heredity* 127, no. 2: 233–244. https://doi.org/10.1038/s41437-021-00446-5.

Cartmill, M. 1974. "Daubentonia, Dactylopsila, Woodpeckers, and Klinorhynchy." In *Prosimian Biology*, edited by R. D. Martin, G. A. Doyle, and A. C. Walker, 655–670. University of Pittsburgh Press.

Castellano, D., M. C. Macià, P. Tataru, T. Bataillon, and K. Munch. 2019. "Comparison of the Full Distribution of Fitness Effects of New Amino Acid Mutations Across Great Apes." *Genetics* 213: 953–966. https://doi.org/10.1534/genetics.119.302494.

Chaignat, E., E. A. Yahya-Graison, C. N. Henrichsen, et al. 2011. "Copy Number Variation Modifies Expression Time Courses." *Genome Research* 21, no. 1: 106–113. https://doi.org/10.1101/gr.112748.110.

Chamary, J., and L. D. Hurst. 2005. "Evidence for Selection on Synonymous Mutations Affecting Stability of mRNA Secondary Structure in Mammals." *Genome Biology* 6: R75. https://doi.org/10.1186/gb-2005-6-9-r75.

Charlesworth, B. 1996. "Background Selection and Patterns of Genetic Diversity in *Drosophila melanogaster*." *Genetical Research* 68: 131–149. https://doi.org/10.1017/s0016672300034029.

Charlesworth, B. 2013. "Background Selection 20 Years On." *Journal of Heredity* 104: 161–171. https://doi.org/10.1093/jhered/ess136.

Charlesworth, D. 2017. "Evolution of Recombination Rates Between Sex Chromosomes." *Philosophical Transactions of the Royal Society, B: Biological Sciences* 372: 20160456. https://doi.org/10.1098/rstb.2016.0456.

Charlesworth, B., D. Charlesworth, and N. H. Barton. 2003. "The Effects of Genetic and Geographic Structure on Neutral Variation." *Annual Review of Ecology, Evolution, and Systematics* 34: 99–125. https://doi.org/10.1146/annurev.ecolsys.34.011802.132359.

Charlesworth, B., and J. D. Jensen. 2021. "Effects of Selection at Linked Sites on Patterns of Genetic Variability." *Annual Review of Ecology, Evolution, and Systematics* 52: 177–197. https://doi.org/10.1146/annurev-ecolsys-010621-044528.

Charlesworth, B., and J. D. Jensen. 2022. "Some Complexities in Interpreting Apparent Effects of Hitchhiking: A Commentary on Gompert et al. (2022)." *Molecular Ecology* 31: 4440–4443. https://doi.org/10.1111/mec.16573.

Charlesworth, B., and J. D. Jensen. 2024. "Population Genetics." In *Encyclopedia of Biodiversity*, 467–483. Elsevier. https://linkinghub.elsevier.com/retrieve/pii/B9780128225622000219.

Charlesworth, B., M. T. Morgan, and D. Charlesworth. 1993. "The Effect of Deleterious Mutations on Neutral Molecular Variation." *Genetics* 134: 1289–1303. https://doi.org/10.1093/genetics/134.4.1289.

Cheng, X., and M. DeGiorgio. 2020. "Flexible Mixture Model Approaches That Accommodate Footprint Size Variability for Robust Detection of Balancing Selection." *Molecular Biology and Evolution* 37: 3267–3291. https://doi.org/10.1093/molbev/msaa134.

Chiang, C., A. J. Scott, J. R. Davis, et al. 2017. "The Impact of Structural Variation on Human Gene Expression." *Nature Genetics* 49, no. 5: 692–699. https://doi.org/10.1038/ng.3834.

Chintalapati, M., and P. Moorjani. 2020. "Evolution of the Mutation Rate Across Primates." *Current Opinion in Genetics & Development* 62: 58–64. https://doi.org/10.1016/j.gde.2020.05.028.

Clark, A. G., X. Wang, and T. Matise. 2010. "Contrasting Methods of Quantifying Fine Structure of Human Recombination." *Annual Review of Genomics and Human Genetics* 11: 45–64. https://doi.org/10.1146/annurev-genom-082908-150031.

Comeron, J. M. 2014. "Background Selection as Baseline for Nucleotide Variation Across the *Drosophila* Genome." *PLoS Genetics* 10: e1004434. https://doi.org/10.1371/journal.pgen.1004434.

Comeron, J. M. 2017. "Background Selection as Null Hypothesis in Population Genomics: Insights and Challenges From *Drosophila* Studies." *Philosophical Transactions of the Royal Society, B: Biological Sciences* 372: 20160471. https://doi.org/10.1098/rstb.2016.0471.

Conrad, D. F., J. E. Keebler, M. A. DePristo, et al. 2011. "Variation in Genome-Wide Mutation Rates Within and Between Human Families." *Nature Genetics* 43, no. 7: 712–714. https://doi.org/10.1038/ng.862.

Conrad, D. F., D. Pinto, R. Redon, et al. 2010. "Origins and Functional Impact of Copy Number Variation in the Human Genome." *Nature* 464, no. 7289: 704–712. https://doi.org/10.1038/nature08516.

Coop, G., X. Wen, C. Ober, J. K. Pritchard, and M. Przeworski. 2008. "High-Resolution Mapping of Crossovers Reveals Extensive Variation in Fine-Scale Recombination Patterns Among Humans." *Science* 319: 1395–1398. https://doi.org/10.1126/science.1151851.

Cox, L. A., M. C. Mahaney, J. L. Vandeberg, and J. Rogers. 2006. "A Second-Generation Genetic Linkage Map of the Baboon (*Papio hamadryas*) Genome." *Genomics* 88, no. 3: 274–281. https://doi.org/10.1016/j.ygeno.2006.03.020.

Crisci, J. L., Y.-P. Poh, A. Bean, A. Simkin, and J. D. Jensen. 2012. "Recent Progress in Polymorphism-Based Population Genetic Inference." *Journal of Heredity* 103, no. 2: 287–296. https://doi.org/10.1093/jhered/esr128.

Crisci, J. L., Y.-P. Poh, S. Mahajan, and J. D. Jensen. 2013. "The Impact of Equilibrium Assumptions on Tests of Selection." *Frontiers in Genetics* 4: 235. https://doi.org/10.3389/fgene.2013.00235.

Crow, J. F. 1987. "Muller, Dobzhansky, and Overdominance." *Journal of the History of Biology* 20, no. 3: 351–380. https://doi.org/10.1007/BF00139460.

Cutter, A. D., and B. A. Payseur. 2013. "Genomic Signatures of Selection at Linked Sites: Unifying the Disparity Among Species." *Nature Reviews Genetics* 14: 262–274. https://doi.org/10.1038/nrg3425.

Dapper, A. L., and B. A. Payseur. 2018. "Effects of Demographic History on the Detection of Recombination Hotspots From Linkage Disequilibrium." *Molecular Biology and Evolution* 35: 335–353. https://doi.org/10.1093/molbev/msx272.

de Filippo, C., F. M. Key, S. Ghirotto, et al. 2016. "Recent Selection Changes in Human Genes Under Long-Term Balancing Selection." *Molecular Biology and Evolution* 33: 1435–1447. https://doi.org/10.1093/molbev/msw023.

DeGiorgio, M., C. D. Huber, M. J. Hubisz, I. Hellmann, and R. Nielsen. 2016. "SweepFinder2: Increased Sensitivity, Robustness and Flexibility." *Bioinformatics* 32: 1895–1897. https://doi.org/10.1093/bioinformatics/btw051.

Dewar, R. E., and A. F. Richard. 2012. "Madagascar: A History of Arrivals, What Happened, and Will Happen Next." *Annual Review of Anthropology* 41: 495–517. https://doi.org/10.1146/annurev-anthro-092611-145758.

Dixson, A., B. Dixson, and M. Anderson. 2005. "Sexual Selection and the Evolution of Visually Conspicuous Sexually Dimorphic Traits in Male Monkeys, Apes, and Human Beings." *Annual Review of Sex Research* 16, no. 1: 1–19. https://doi.org/10.1080/10532528.2005.10559826.

Dutheil, J. Y. 2024. "On the Estimation of Genome-Average Recombination Rates." *Genetics* 227: iyae051. https://doi.org/10.1093/genetics/iyae051.

Eggertsson, H. P., H. Jonsson, S. Kristmundsdottir, et al. 2017. "Graphtyper Enables Population-Scale Genotyping Using Pangenome Graphs." *Nature Genetics* 49, no. 11: 1654–1660. https://doi.org/10.1038/ng.3964.

Ellegren, H. 2011. "Sex-Chromosome Evolution: Recent Progress and the Influence of Male and Female Heterogamety." *Nature Reviews Genetics* 12: 157–166. https://doi.org/10.1038/nrg2948.

Ewing, G. B., and J. D. Jensen. 2014. "Distinguishing Neutral From Deleterious Mutations in Growing Populations." *Frontiers in Genetics* 5: 7. https://doi.org/10.3389/fgene.2014.00007.

Ewing, G. B., and J. D. Jensen. 2016. "The Consequences of Not Accounting for Background Selection in Demographic Inference." *Molecular Ecology* 25, no. 1: 135–141. https://doi.org/10.1111/mec.13390.

Excoffier, L., I. Dupanloup, E. Huerta-Sánchez, V. C. Sousa, and M. Foll. 2013. "Robust Demographic Inference From Genomic and SNP Data." *PLoS Genetics* 9: e1003905. https://doi.org/10.1371/journal.pgen.1003905.

Eyre-Walker, A., and P. D. Keightley. 2007. "The Distribution of Fitness Effects of New Mutations." *Nature Reviews Genetics* 8, no. 8: 610–618. https://doi.org/10.1038/nrg2146.

Eyre-Walker, A., and P. D. Keightley. 2009. "Estimating the Rate of Adaptive Molecular Evolution in the Presence of Slightly Deleterious Mutations and Population Size Change." *Molecular Biology and Evolution* 26: 2097–2108. https://doi.org/10.1093/molbev/msp119.

Felsenstein, J. 1974. "The Evolutionary Advantage of Recombination." *Genetics* 78: 737–756. https://doi.org/10.1093/genetics/78.2.737.

Fijarczyk, A., and W. Babik. 2015. "Detecting Balancing Selection in Genomes: Limits and Prospects." *Molecular Ecology* 24: 3529–3545. https://doi.org/10.1111/mec.13226.

Francioli, L. C., P. P. Polak, A. Koren, et al. 2015. "Genome-Wide Patterns and Properties of *De Novo* Mutations in Humans." *Nature Genetics* 47, no. 7: 822–826. https://doi.org/10.1038/ng.3292.

Galtier, N. 2016. "Adaptive Protein Evolution in Animals and the Effective Population Size Hypothesis." *PLoS Genetics* 12: e1005774. https://doi.org/10.1371/journal.pgen.1005774.

Ganzhorn, J. U., J. P. Abraham, and M. Razanahoera-Rakotomalala. 1985. "Some Aspects of the Natural History and Food Selection of Avahi Laniger." *Primates* 26, no. 4: 452–463. https://doi.org/10.1007/BF02382459.

George, R. D., G. McVicker, R. Diederich, et al. 2011. "*Trans* Genomic Capture and Sequencing of Primate Exomes Reveals New Targets of Positive Selection." *Genome Research* 21: 1686–1694. https://doi.org/10.1101/gr.121327.111.

Ghafoor, S., J. Santos, C. J. Versoza, J. D. Jensen, and S. P. Pfeifer. 2023. "The Impact of Sample Size and Population History on Observed Mutational Spectra: A Case Study in Human and Chimpanzee Populations." *Genome Biology and Evolution* 15, no. 3: evad019. https://doi.org/10.1093/gbe/evad019.

Goldmann, J. M., W. S. W. Wong, M. Pinelli, et al. 2016. "Parent-of-Origin-Specific Signatures of *De Novo* Mutations." *Nature Genetics* 48, no. 8: 935–939. https://doi.org/10.1038/ng.3597.

Gotch, A. 1995. *Latin Names Explained: A Guide to the Scientific Classification of Reptiles, Birds & Mammals*. Blandford Press.

Gross, M. 2017. "Primates in Peril." *Current Biology* 27: R573–R576. https://doi.org/10.1016/j.cub.2017.06.002.

Gutenkunst, R. N., R. D. Hernandez, S. H. Williamson, and C. D. Bustamante. 2009. "Inferring the Joint Demographic History of

Multiple Populations From Multidimensional SNP Frequency Data." *PLoS Genetics* 5: e1000695. https://doi.org/10.1371/journal.pgen.1000695.

Haldane, J. B. S. 1932. *The Causes of Evolution*. Longmans, Green, & Co.

Haldane, J. B. S. 1935. "The Rate of Spontaneous Mutation of a Human Gene." *Journal of Genetics* 31: 317–326. https://doi.org/10.1007/BF02982403.

Halldorsson, B. V., M. T. Hardarson, B. Kehr, et al. 2016. "The Rate of Meiotic Gene Conversion Varies by Sex and Age." *Nature Genetics* 48: 1377–1384. https://doi.org/10.1038/ng.3669.

Hansford, J. P., P. C. Wright, V. R. Pérez, K. M. Muldoon, S. T. Turvey, and L. R. Godfrey. 2020. "Evidence for Early Human Arrival in Madagascar Is Robust: A Response to Mitchell." *Journal of Island and Coastal Archaeology* 15: 596–602. https://doi.org/10.1080/15564894.2020.1771482.

Harris, R. B., and J. D. Jensen. 2020. "Considering Genomic Scans for Selection as Coalescent Model Choice." *Genome Biology and Evolution* 12: 871–877. https://doi.org/10.1093/gbe/evaa093.

Harris, R. B., A. Sackman, and J. D. Jensen. 2018. "On the Unfounded Enthusiasm for Soft Selective Sweeps II: Examining Recent Evidence From Humans, Flies, and Viruses." *PLoS Genetics* 14: e1007859. https://doi.org/10.1371/journal.pgen.1007859.

Hartwig, W. 2011. "Chapter 3: Primate Evolution." In *Primates in Perspective*, edited by C. J. Campbell, et al., 19–31. 2nd ed. Oxford University Press.

Hill, W. G., and A. Robertson. 1966. "The Effect of Linkage on Limits to Artificial Selection." *Genetical Research* 8: 269–294. https://doi.org/10.1017/s001667230800949x.

Hodgkinson, A., and A. Eyre-Walker. 2011. "Variation in the Mutation Rate Across Mammalian Genomes." *Nature Reviews Genetics* 12: 756–766. https://doi.org/10.1038/nrg3098.

Horvath, J. E., D. W. Weisrock, S. L. Embry, et al. 2008. "Development and Application of a Phylogenomic Toolkit: Resolving the Evolutionary History of Madagascar's Lemurs." *Genome Research* 18: 489–499. https://doi.org/10.1101/gr.7265208.

Howell, A. A., J. W. Terbot, V. Soni, P. Johri, J. D. Jensen, and S. P. Pfeifer. 2023. "Developing an Appropriate Evolutionary Baseline Model for the Study of Human Cytomegalovirus." *Genome Biology and Evolution* 15: evad059. https://doi.org/10.1093/gbe/evad059.

Hwang, D. G., and P. Green. 2004. "Bayesian Markov Chain Monte Carlo Sequence Analysis Reveals Varying Neutral Substitution Patterns in Mammalian Evolution." *Proceedings of the National Academy of Sciences of the United States of America* 101: 13994–14001. https://doi.org/10.1073/pnas.0404142101.

Irwin, K. K., S. Laurent, S. Matuszewski, et al. 2016. "On the Importance of Skewed Offspring Distributions and Background Selection in Virus Population Genetics." *Heredity* 117: 393–399. https://doi.org/10.1038/hdy.2016.58.

Itsara, A., H. Wu, J. D. Smith, et al. 2010. "*De Novo* Rates and Selection of Large Copy Number Variation." *Genome Research* 20, no. 11: 1469–1481. https://doi.org/10.1101/gr.107680.110.

IUCN. 2024. *The IUCN Red List of Threatened Species*. Version 2024-1. IUCN. https://www.iucnredlist.org.

Jasinska, A. J., S. Service, M. Levinson, et al. 2007. "A Genetic Linkage Map of the Vervet Monkey (*Chlorocebus aethiops sabaeus*)." *Mammalian Genome* 18, no. 5: 347–360. https://doi.org/10.1007/s00335-007-9026-4.

Jeffreys, A. J., and C. A. May. 2004. "Intense and Highly Localized Gene Conversion Activity in Human Meiotic Crossover Hot Spots." *Nature Genetics* 36, no. 2: 151–156. https://doi.org/10.1038/ng1287.

Jensen, J. D. 2021. "Studying Population Genetic Processes in Viruses: From Drug-Resistance Evolution to Patient Infection Dynamics." In *Encyclopedia of Virology*, edited by D. H. Bamford and M. Zuckerman, 227–232. Elsevier. https://doi.org/10.1016/B978-0-12-814515-9.00113-2.

Jensen, J. D. 2023. "Population Genetic Concerns Related to the Interpretation of Empirical Outliers and the Neglect of Common Evolutionary Processes." *Heredity* 130: 109–110. https://doi.org/10.1038/s41437-022-00575-5.

Jensen, J. D., Y. Kim, V. B. DuMont, C. F. Aquadro, and C. D. Bustamante. 2005. "Distinguishing Between Selective Sweeps and Demography Using DNA Polymorphism Data." *Genetics* 170: 1401–1410. https://doi.org/10.1534/genetics.104.038224.

Jensen, J. D., B. A. Payseur, W. Stephan, et al. 2019. "The Importance of the Neutral Theory in 1968 and 50 Years on: A Response to Kern and Hahn 2018." *Evolution* 73, no. 1: 111–114. https://doi.org/10.1111/evo.13650.

Jensen, J. D., K. R. Thornton, C. D. Bustamante, and C. F. Aquadro. 2007. "On the Utility of Linkage Disequilibrium as a Statistic for Identifying Targets of Positive Selection in Nonequilibrium Populations." *Genetics* 176, no. 4: 2371–2379. https://doi.org/10.1534/genetics.106.069450.

Johri, P., C. F. Aquadro, M. Beaumont, et al. 2022. "Recommendations for Improving Statistical Inference in Population Genomics." *PLoS Biology* 20: e3001669. https://doi.org/10.1371/journal.pbio.3001669.

Johri, P., B. Charlesworth, and J. D. Jensen. 2020. "Toward an Evolutionarily Appropriate Null Model: Jointly Inferring Demography and Purifying Selection." *Genetics* 215: 173–192. https://doi.org/10.1534/genetics.119.303002.

Johri, P., A. Eyre-Walker, R. N. Gutenkunst, K. E. Lohmueller, and J. D. Jensen. 2022. "On the Prospect of Achieving Accurate Joint Estimation of Selection With Population History." *Genome Biology and Evolution* 14: evac088. https://doi.org/10.1093/gbe/evac088.

Johri, P., S. P. Pfeifer, and J. D. Jensen. 2023. "Developing an Evolutionary Baseline Model for Humans: Jointly Inferring Purifying Selection With Population History." *Molecular Biology and Evolution* 40: msad100. https://doi.org/10.1093/molbev/msad100.

Johri, P., K. Riall, H. Becher, L. Excoffier, B. Charlesworth, and J. D. Jensen. 2021. "The Impact of Purifying and Background Selection on the Inference of Population History: Problems and Prospects." *Molecular Biology and Evolution* 38: 2986–3003. https://doi.org/10.1093/molbev/msab050.

Jónsson, H., P. Sulem, B. Kehr, et al. 2017. "Parental Influence on Human Germline *De Novo* Mutations in 1,548 Trios From Iceland." *Nature* 549, no. 7673: 519–522. https://doi.org/10.1038/nature24018.

Kaiser, V. B., and B. Charlesworth. 2009. "The Effects of Deleterious Mutations on Evolution in Non-Recombining Genomes." *Trends in Genetics* 25: 9–12. https://doi.org/10.1016/j.tig.2008.10.009.

Keightley, P. D., and A. Eyre-Walker. 2010. "What Can We Learn About the Distribution of Fitness Effects of New Mutations From DNA Sequence Data." *Philosophical Transactions of the Royal Society, B: Biological Sciences* 365, no. 1544: 1187–1193. https://doi.org/10.1098/rstb.2009.0266.

Keinan, A., J. C. Mullikin, N. Patterson, and D. Reich. 2009. "Accelerated Genetic Drift on Chromosome X During the Human Dispersal Out of Africa." *Nature Genetics* 41: 66–70. https://doi.org/10.1038/ng.303.

Kessler, M. D., D. P. Loesch, J. A. Perry, et al. 2020. "*De Novo* Mutations Across 1,465 Diverse Genomes Reveal Mutational Insights and Reductions in the Amish Founder Population." *Proceedings of the National Academy of Sciences of the United States of America* 117, no. 5: 2560–2569. https://doi.org/10.1073/pnas.1902766117.

Kim, Y. 2006. "Allele Frequency Distribution Under Recurrent Selective Sweeps." *Genetics* 172: 1967–1978. https://doi.org/10.1534/genetics.105.048447.

Kim, Y., and W. Stephan. 2002. "Detecting a Local Signature of Genetic Hitchhiking Along a Recombining Chromosome." *Genetics* 160: 765–777. https://doi.org/10.1093/genetics/160.2.765.

Kimura, M. 1968. "Evolutionary Rate at the Molecular Level." *Nature* 217: 624–626. https://doi.org/10.1038/217624a0.

Kimura, M. 1983. *The Neutral Theory of Molecular Evolution*. 1st ed. Cambridge University Press. https://www.cambridge.org/core/product/identifier/9780511623486/type/book.

Kong, A., M. L. Frigge, G. Masson, et al. 2012. "Rate of *De Novo* Mutations and the Importance of Father's Age to Disease Risk." *Nature* 488, no. 7412: 471–475. https://doi.org/10.1038/nature11396.

Kong, A., D. F. Gudbjartsson, J. Sainz, et al. 2002. "A High-Resolution Recombination Map of the Human Genome." *Nature Genetics* 31: 241–247. https://doi.org/10.1038/ng917.

Kong, A., G. Thorleifsson, D. F. Gudbjartsson, et al. 2010. "Fine-Scale Recombination Rate Differences Between Sexes, Populations and Individuals." *Nature* 467: 1099–1103. https://doi.org/10.1038/nature09525.

Kuderna, L. F. K., H. Gao, M. C. Janiak, et al. 2023. "A Global Catalog of Whole-Genome Diversity From 233 Primate Species." *Science* 380, no. 6648: 906–913. https://doi.org/10.1126/science.abn7829.

Lewontin, R. C. 1987. "Polymorphism and Heterosis: Old Wine in New Bottles and Vice Versa." *Journal of the History of Biology* 20, no. 3: 337–349. https://doi.org/10.1007/BF00139459.

Lewontin, R. C., and J. Krakauer. 1973. "Distribution of Gene Frequency as a Test of the Theory of the Selective Neutrality of Polymorphisms." *Genetics* 74: 175–195. https://doi.org/10.1093/genetics/74.1.175.

Litman, B. J., and C. D. Mitchell. 1996. "Rhodopsin Structure and Function." In *Biomembranes: A Multi-Volume Treatise*, edited by A. G. Lee, Vol. 2, 1–32. Elsevier.

Louis, E. E., T. M. Sefczek, D. R. Randimbiharinirina, et al. 2020. *Daubentonia madagascariensis*. IUCN Red List. https://doi.org/10.2305/IUCN.UK.2020-2.RLTS.T6302A115560793.en.

Lynch, M. 2010. "Evolution of the Mutation Rate." *Trends in Genetics* 26: 345–352. https://doi.org/10.1016/j.tig.2010.05.003.

Mao, Y., W. T. Harvey, D. Porubsky, et al. 2024. "Structurally Divergent and Recurrently Mutated Regions of Primate Genomes." *Cell* 187, no. 6: 1547–1562.e13. https://doi.org/10.1016/j.cell.2024.01.052.

Margalit, M., L. Yogev, H. Yavetz, et al. 2012. "Involvement of the Prostate and Testis Expression (PATE)-Like Proteins in Sperm-Oocyte Interaction." *Human Reproduction* 27, no. 5: 1238–1248. https://doi.org/10.1093/humrep/des064.

Martin, R. D. 1990. *Primate Origins and Evolution: A Phylogenetic Reconstruction*. Princeton University Press.

Martinez, G., and C. Garcia. 2020. "Sexual Selection and Sperm Diversity in Primates." *Molecular and Cellular Endocrinology* 518: 110974. https://doi.org/10.1016/j.mce.2020.110974.

Maynard Smith, J., and J. Haigh. 1974. "The Hitch-Hiking Effect of a Favourable Gene." *Genetical Research* 23: 23–35. https://doi.org/10.1017/s0016672308009579.

McLain, A. T., T. J. Meyer, C. Faulk, et al. 2012. "An Alu-Based Phylogeny of Lemurs (Infraorder: Lemuriformes)." *PLoS One* 7: e44035. https://doi.org/10.1371/journal.pone.0044035.

Michaelson, J. J., Y. Shi, M. Gujral, et al. 2012. "Whole-Genome Sequencing in Autism Identifies Hot Spots for *De Novo* Germline Mutation." *Cell* 151, no. 7: 1431–1442. https://doi.org/10.1016/j.cell.2012.11.019.

Mills, R. E., W. S. Pittard, J. M. Mullaney, et al. 2011. "Natural Genetic Variation Caused by Small Insertions and Deletions in the Human Genome." *Genome Research* 21, no. 6: 830–839. https://doi.org/10.1101/gr.115907.110.

Mittermeier, R., E. Louis, Jr., M. Richardson, et al. 2010. *Lemurs of Madagascar*. 3rd ed. Conservation International.

Moorjani, P., C. E. G. Amorim, P. F. Arndt, and M. Przeworski. 2016. "Variation in the Molecular Clock of Primates." *Proceedings of the National Academy of Sciences of the United States of America* 113: 10607–10612. https://doi.org/10.1073/pnas.1600374113.

Morales-Arce, A. Y., P. Johri, and J. D. Jensen. 2022. "Inferring the Distribution of Fitness Effects in Patient-Sampled and Experimental Virus Populations: Two Case Studies." *Heredity* 128: 79–87. https://doi.org/10.1038/s41437-021-00493-y.

Nachman, M. W., and S. L. Crowell. 2000. "Estimate of the Mutation Rate Per Nucleotide in Humans." *Genetics* 156, no. 1: 297–304. https://doi.org/10.1093/genetics/156.1.297.

Nicolaisen, L. E., and M. M. Desai. 2012. "Distortions in Genealogies Due to Purifying Selection." *Molecular Biology and Evolution* 29: 3589–3600. https://doi.org/10.1093/molbev/mss170.

Nicolaisen, L. E., and M. M. Desai. 2013. "Distortions in Genealogies Due to Purifying Selection and Recombination." *Genetics* 195: 221–230. https://doi.org/10.1534/genetics.113.152983.

Nielsen, R., S. Williamson, Y. Kim, M. J. Hubisz, A. G. Clark, and C. Bustamante. 2005. "Genomic Scans for Selective Sweeps Using SNP Data." *Genome Research* 15: 1566–1575. https://doi.org/10.1101/gr.4252305.

O'Fallon, B. D., J. Seger, and F. R. Adler. 2010. "A Continuous-State Coalescent and the Impact of Weak Selection on the Structure of Gene Genealogies." *Molecular Biology and Evolution* 27: 1162–1172. https://doi.org/10.1093/molbev/msq006.

Olito, C., and J. K. Abbott. 2025. "The Evolution of Suppressed Recombination Between Sex Chromosomes and the Lengths of Evolutionary Strata." *Evolution* 79: 1371–1385. https://doi.org/10.1093/evolut/qpaf045.

Paigen, K., and P. Petkov. 2010. "Mammalian Recombination Hot Spots: Properties, Control and Evolution." *Nature Reviews Genetics* 11: 221–233. https://doi.org/10.1038/nrg2712.

Palsson, G., M. T. Hardarson, H. Jonsson, et al. 2025. "Complete Human Recombination Maps." *Nature* 639: 700–707. https://doi.org/10.1038/s41586-024-08450-5.

Pang, A. W., J. R. MacDonald, D. Pinto, et al. 2010. "Towards a Comprehensive Structural Variation Map of an Individual Human Genome." *Genome Biology* 11: R52. https://doi.org/10.1186/gb-2010-11-5-r52.

Peñalba, J. V., and J. B. W. Wolf. 2020. "From Molecules to Populations: Appreciating and Estimating Recombination Rate Variation." *Nature Reviews Genetics* 21: 476–492. https://doi.org/10.1038/s41576-020-0240-1.

Perelman, P., W. E. Johnson, C. Roos, et al. 2011. "A Molecular Phylogeny of Living Primates." *PLoS Genetics* 7: e1001342. https://doi.org/10.1371/journal.pgen.1001342.

Perry, G. H., E. E. Louis, A. Ratan, et al. 2013. "Aye-Aye Population Genomic Analyses Highlight an Important Center of Endemism in Northern Madagascar." *Proceedings of the National Academy of Sciences of the United States of America* 110: 5823–5828. https://doi.org/10.1073/pnas.1211990110.

Perry, G. H., R. D. Martin, and B. C. Verrelli. 2007. "Signatures of Functional Constraint at Aye-Aye Opsin Genes: The Potential of Adaptive Color Vision in a Nocturnal Primate." *Molecular Biology and Evolution* 24: 1963–1970. https://doi.org/10.1093/molbev/msm124.

Perry, G. H., P. Melsted, J. C. Marioni, et al. 2012. "Comparative RNA Sequencing Reveals Substantial Genetic Variation in Endangered

Primates." *Genome Research* 22: 602–610. https://doi.org/10.1101/gr.130468.111.

Perry, G. H., D. Reeves, P. Melsted, et al. 2012. "A Genome Sequence Resource for the Aye-Aye (*Daubentonia madagascariensis*), a Nocturnal Lemur From Madagascar." *Genome Biology and Evolution* 4: 126–135. https://doi.org/10.1093/gbe/evr132.

Pfeifer, S. P. 2017a. "From Next-Generation Resequencing Reads to a High-Quality Variant Data Set." *Heredity* 118: 111–124. https://doi.org/10.1038/hdy.2016.102.

Pfeifer, S. P. 2017b. "Direct Estimate of the Spontaneous Germ Line Mutation Rate in African Green Monkeys." *Evolution* 71: 2858–2870. https://doi.org/10.1111/evo.13383.

Pfeifer, S. P. 2020a. "Spontaneous Mutation Rates." In *The Molecular Evolutionary Clock: Theory and Practice*, edited by S. Y. W. Ho, 35–44. Springer Nature. https://doi.org/10.1093/gbe/evw240.

Pfeifer, S. P. 2020b. "A Fine-Scale Genetic Map for Vervet Monkeys." *Molecular Biology and Evolution* 37, no. 7: 1855–1865. https://doi.org/10.1093/molbev/msaa079.

Pfeifer, S. P., and J. D. Jensen. 2016. "The Impact of Linked Selection in Chimpanzees: A Comparative Study." *Genome Biology and Evolution* 8: 3202–3208. https://doi.org/10.1093/gbe/evw240.

Poh, Y.-P., V. S. Domingues, H. E. Hoekstra, and J. D. Jensen. 2014. "On the Prospect of Identifying Adaptive Loci in Recently Bottlenecked Populations." *PLoS One* 9: e110579. https://doi.org/10.1371/journal.pone.0110579.

Porubsky, D., H. Dashnow, T. A. Sasani, et al. 2025. "Human *De Novo* Mutation Rates From a Four-Generation Pedigree Reference." *Nature* 643, no. 8071: 427–436. https://doi.org/10.1038/s41586-025-08922.

Pozzi, L., J. A. Hodgson, A. S. Burrell, K. N. Sterner, R. L. Raaum, and T. R. Disotell. 2014. "Primate Phylogenetic Relationships and Divergence Dates Inferred From Complete Mitochondrial Genomes." *Molecular Phylogenetics and Evolution* 75: 165–183.

Prado-Martinez, J., P. H. Sudmant, J. M. Kidd, et al. 2013. "Great Ape Genetic Diversity and Population History." *Nature* 499: 471–475. https://doi.org/10.1038/nature12228.

Pratto, F., K. Brick, P. Khil, F. Smagulova, G. V. Petukhova, and R. D. Camerini-Otero. 2014. "Recombination Initiation Maps of Individual Human Genomes." *Science* 346: 1256442. https://doi.org/10.1126/science.1256442.

Price, E. C., and A. T. C. Feistner. 1994. "Responses of Captive Aye-Ayes (*Daubentonia madagascariensis*) to the Scent of Conspecifics: A Preliminary Investigation." *Folia Primatologica* 62: 170–174. https://doi.org/10.1159/000156774.

Quinn, A., and D. E. Wilson. 2004. "Daubentonia madagascariensis." *Mammalian Species* 740: 1–6. https://doi.org/10.1644/740.

Rahbari, R., A. Wuster, S. J. Lindsay, et al. 2016. "Timing, Rates and Spectra of Human Germline Mutation." *Nature Genetics* 48, no. 2: 126–133. https://doi.org/10.1038/ng.3469.

Rausell, A., and A. Telenti. 2014. "Genomics of Host–Pathogen Interactions." *Current Opinion in Immunology* 30: 32–38. https://doi.org/10.1016/j.coi.2014.06.001.

Redon, R., S. Ishikawa, K. R. Fitch, et al. 2006. "Global Variation in Copy Number in the Human Genome." *Nature* 444: 444–454. https://doi.org/10.1038/nature05329.

Ritz, K. R., M. A. F. Noor, and N. D. Singh. 2017. "Variation in Recombination Rate: Adaptive or Not." *Trends in Genetics* 33: 364–374. https://doi.org/10.1016/j.tig.2017.03.003.

Roach, J. C., G. Glusman, A. F. A. Smit, et al. 2010. "Analysis of Genetic Inheritance in a Family Quartet by Whole-Genome Sequencing." *Science* 328, no. 5978: 636–639. https://doi.org/10.1126/science.1186802.

Rogers, J., R. Garcia, W. Shelledy, et al. 2006. "An Initial Genetic Linkage Map of the Rhesus Macaque (*Macaca mulatta*) Genome Using Human Microsatellite Loci." *Genomics* 87: 30–38. https://doi.org/10.1016/j.ygeno.2005.10.004.

Rogers, J., M. C. Mahaney, S. M. Witte, et al. 2000. "A Genetic Linkage Map of the Baboon (*Papio hamadryas)* Genome Based on Human Microsatellite Polymorphisms." *Genomics* 67: 237–247. https://doi.org/10.1006/geno.2000.6245.

Ross, C. 2003. "Life History, Infant Care Strategies, and Brain Size in Primates." In *Primate Life Histories and Socioecology*, edited by P. M. Kappeler and M. E. Pereira, 266–284. Chicago University Press.

Sackman, A. M., R. B. Harris, and J. D. Jensen. 2019. "Inferring Demography and Selection in Organisms Characterized by Skewed Offspring Distributions." *Genetics* 211, no. 3: 1019–1028. https://doi.org/10.1534/genetics.118.301684.

Salmona, J., R. Heller, E. Quéméré, and L. Chikhi. 2017. "Climate Change and Human Colonization Triggered Habitat Loss and Fragmentation in Madagascar." *Molecular Ecology* 26: 5203–5222. https://doi.org/10.1111/mec.14173.

Samuk, K., and M. A. F. Noor. 2022. "Gene Flow Biases Population Genetic Inference of Recombination Rate." *G3: Genes|Genomes|Genetics* 12, no. 11: jkac236. https://doi.org/10.1093/g3journal/jkac236.

Sasani, T. A., B. S. Pedersen, Z. Gao, et al. 2019. "Large, Three-Generation Human Families Reveal Post-Zygotic Mosaicism and Variability in Germline Mutation Accumulation." *eLife* 8: e46922. https://doi.org/10.7554/eLife.46922.

Schneider, A., B. Charlesworth, A. Eyre-Walker, and P. D. Keightley. 2011. "A Method for Inferring the Rate of Occurrence and Fitness Effects of Advantageous Mutations." *Genetics* 189: 1427–1437. https://doi.org/10.1534/genetics.111.131730.

Schülke, O. 2005. "Evolution of Pair-Living in *Phaner furcifer*." *International Journal of Primatology* 26: 903–919. https://doi.org/10.1007/s10764-005-5328-0.

Schwitzer, C., Mittermeier, R. A., Davies, N., et al. 2013. *Lemurs of Madagascar: A Strategy for Their Conservation 2013–2016*, 185. IUCN SSC Primate Specialist Group, Bristol Conservation and Science Foundation, and Conservation International. ISBN: 978-1-934151-62-4.

Ségurel, L., M. J. Wyman, and M. Przeworski. 2014. "Determinants of Mutation Rate Variation in the Human Germline." *Annual Review of Genomics and Human Genetics* 15: 47–70. https://doi.org/10.1146/annurev-genom-031714-125740.

Shao, Y., L. Zhou, F. Li, et al. 2023. "Phylogenomic Analyses Provide Insights Into Primate Evolution." *Science* 380: 913–924. https://doi.org/10.1126/science.abn6919.

Simons, E. L. 1995. "History, Anatomy, Subfossil Record and Management of *Daubentonia madagascariensis*." In *Creatures of the Dark: The Nocturnal Prosimians*, edited by L. Alterman, G. A. Doyle, and M. K. Izard, 133–140. Plenum Press.

Simonsen, K. L., G. A. Churchill, and C. F. Aquadro. 1995. "Properties of Statistical Tests of Neutrality for DNA Polymorphism Data." *Genetics* 141: 413–429. https://doi.org/10.1093/genetics/141.1.413.

Singh, N. D., J. M. Macpherson, J. D. Jensen, and D. A. Petrov. 2007. "Similar Levels of X-Linked and Autosomal Nucleotide Variation in African and Non-African Populations of *Drosophila melanogaster*." *BMC Evolutionary Biology* 7: 202. https://doi.org/10.1186/1471-2148-7-202.

Smith, R. J., and W. L. Jungers. 1997. "Body Mass in Comparative Primatology." *Journal of Human Evolution* 32, no. 6: 523–559. https://doi.org/10.1006/jhev.1996.0122.

Soler-García, A., R. Maitra, V. Kumar, et al. 2005. "The PATE Gene Is Expressed in the Accessory Tissues of the Human Male Genital Tract

and Encodes a Secreted Sperm-Associated Protein." *Reproduction* 129, no. 4: 515–524. https://doi.org/10.1530/rep.1.00576.

Soni, V., and J. D. Jensen. 2024. "Temporal Challenges in Detecting Balancing Selection From Population Genomic Data." *G3: Genes, Genomes, Genetics* 14: jkae069. https://doi.org/10.1093/g3journal/jkae069.

Soni, V., and J. D. Jensen. 2025. "Inferring Demographic and Selective Histories From Population Genomic Data Using a 2-Step Approach in Species With Coding-Sparse Genomes: An Application to Human Data." *G3: Genes, Genomes, Genetics* 15: jkaf019. https://doi.org/10.1093/g3journal/jkaf019.

Soni, V., P. Johri, and J. D. Jensen. 2023. "Evaluating Power to Detect Recurrent Selective Sweeps Under Increasingly Realistic Evolutionary Null Models." *Evolution* 77: 2113–2127. https://doi.org/10.1093/evolut/qpad120.

Soni, V., S. P. Pfeifer, and J. D. Jensen. 2024. "The Effects of Mutation and Recombination Rate Heterogeneity on the Inference of Demography and the Distribution of Fitness Effects." *Genome Biology and Evolution* 16: evae004. https://doi.org/10.1093/gbe/evae004.

Soni, V., J. W. Terbot, and J. D. Jensen. 2024. "Population Genetic Considerations Regarding the Interpretation of Within-Patient SARS-CoV-2 Polymorphism Data." *Nature Communications* 15: 3240. https://doi.org/10.1038/s41467-024-46261-4.

Soni, V., J. W. Terbot, C. J. Versoza, S. P. Pfeifer, and J. D. Jensen. 2025. "A Whole-Genome Scan for Evidence of Positive and Balancing Selection in Aye-Ayes (*Daubentonia madagascariensis*) Utilizing a Well-Fit Evolutionary Baseline Model." *G3: Genes|Genomes|Genetics* 15: jkaf078.

Soni, V., C. J. Versoza, J. D. Jensen, and S. P. Pfeifer. 2025. "Inferring the Landscapes of Mutation and Recombination in the Common Marmoset (*Callithrix jacchus*) in the Presence of Twinning and Hematopoietic Chimerism." Preprint, bioRxiv. https://doi.org/10.1101/2025.07.01.662565.

Soni, V., C. J. Versoza, S. P. Pfeifer, and J. D. Jensen 2025a. "Investigating the Effects of Chimerism on the Inference of Selection: Quantifying Genomic Targets of Purifying, Positive, and Balancing Selection in Common Marmosets (*Callithrix jacchus*)." *Heredity* 134: 645–657. https://doi.org/10.1038/s41437-025-00804-7.

Soni, V., C. J. Versoza, S. P. Pfeifer, and J. D. Jensen. 2025b. "Estimating the Distribution of Fitness Effects in Aye-Ayes (*Daubentonia Madagascariensis*), Accounting for Population History as Well as Mutation and Recombination Rate Heterogeneity." *American Journal of Primatology* 87: e70058. https://doi.org/10.1002/ajp.70058.

Soni, V., C. J. Versoza, J. W. Terbot, J. D. Jensen, and S. P. Pfeifer. 2025. "Inferring Fine-Scale Mutation and Recombination Rate Maps in Aye-Ayes (*Daubentonia madagascariensis*)." *Ecology and Evolution* 15: e72314. https://doi.org/10.1002/ece3.72314.

Soni, V., C. J. Versoza, E. J. Vallender, J. D. Jensen, and S. P. Pfeifer. 2025. "Accounting for Chimerism in Demographic Inference: Reconstructing the History of Common Marmosets (*Callithrix jacchus*) From High-Quality, Whole-Genome, Population-Level Data." *Molecular Biology and Evolution* 42: msaf119. https://doi.org/10.1093/molbev/msaf119.

Spence, J. P., and Y. S. Song. 2019. "Inference and Analysis of Population-Specific Fine-Scale Recombination Maps Across 26 Diverse Human Populations." *Science Advances* 5: eaaw9206. https://doi.org/10.1126/sciadv.aaw9206.

Stapley, J., P. G. D. Feulner, S. E. Johnston, A. W. Santure, and C. M. Smadja. 2017. "Variation in Recombination Frequency and Distribution Across Eukaryotes: Patterns and Processes." *Philosophical Transactions of the Royal Society, B: Biological Sciences* 372: 20160455. https://doi.org/10.1098/rstb.2016.0455.

Sterling, E. 1994. "Taxonomy and Distribution of *Daubentonia*: A Historical Perspective." *Folia Primatologica* 62, no. 1–3: 8–13. https://doi.org/10.1159/000156758.

Stevison, L. S., A. E. Woerner, J. M. Kidd, et al. 2016. "The Time Scale of Recombination Rate Evolution in Great Apes." *Molecular Biology and Evolution* 33: 928–945. https://doi.org/10.1093/molbev/msv331.

Stumpf, M. P. H., and G. A. T. McVean. 2003. "Estimating Recombination Rates From Population-Genetic Data." *Nature Reviews Genetics* 4: 959–968. https://doi.org/10.1038/nrg1227.

Sudmant, P. H., J. Huddleston, C. R. Catacchio, et al. 2013. "Evolution and Diversity of Copy Number Variation in the Great Ape Lineage." *Genome Research* 23, no. 9: 1373–1382. https://doi.org/10.1101/gr.158543.113.

Sudmant, P. H., J. O. Kitzman, F. Antonacci, et al. 2010. "Diversity of Human Copy Number Variation and Multicopy Genes." *Science* 330, no. 6004: 641–646. https://doi.org/10.1126/science.1197005.

Sudmant, P. H., S. Mallick, B. J. Nelson, et al. 2015. "Global Diversity, Population Stratification, and Selection of Human Copy-Number Variation." *Science* 349, no. 6253: aab3761. https://doi.org/10.1126/science.aab3761.

Sudmant, P. H., T. Rausch, E. J. Gardner, et al. 2015. "An Integrated Map of Structural Variation in 2,504 Human Genomes." *Nature* 526, no. 7571: 75–81. https://doi.org/10.1038/nature15394.

Suzzi-Simmons, A. 2023. "Status of Deforestation of Madagascar." *Global Ecology and Conservation* 42: e02389. https://doi.org/10.1016/j.gecco.2023.e02389.

Tataru, P., M. Mollion, S. Glémin, and T. Bataillon. 2017. "Inference of Distribution of Fitness Effects and Proportion of Adaptive Substitutions From Polymorphism Data." *Genetics* 207: 1103–1119. https://doi.org/10.1534/genetics.117.300323.

Tatsumoto, S., Y. Go, K. Fukuta, et al. 2017. "Direct Estimation of *De Novo* Mutation Rates in a Chimpanzee Parent-Offspring Trio by Ultra-Deep Whole Genome Sequencing." *Scientific Reports* 7, no. 1: 13561. https://doi.org/10.1038/s41598-017-13919-7.

Tavaré, S., C. R. Marshall, O. Will, C. Soligo, and R. D. Martin. 2002. "Using the Fossil Record to Estimate the Age of the Last Common Ancestor of Extant Primates." *Nature* 416, no. 6882: 726–729.

Taylor, M. S., C. P. Ponting, and R. R. Copley. 2004. "Occurrence and Consequences of Coding Sequence Insertions and Deletions in Mammalian Genomes." *Genome Research* 14, no. 4: 555–566. https://doi.org/10.1101/gr.1977804.

Terbot, J. W., A. Calahorra-Oliart, C. J. Versoza, et al. 2025. "Re-Evaluating the Demographic History of, and Inferring the Fine-Scale Recombination Landscape for, Wild Chinese Rhesus Macaques (*Macaca mulatta*)." *American Journal of Primatology* 87: e70088. https://doi.org/10.1002/ajp.70088.

Terbot, J. W., B. S. Cooper, J. M. Good, and J. D. Jensen. 2023. "A Simulation Framework for Modeling the Within-Patient Evolutionary Dynamics of SARS-CoV-2." *Genome Biology and Evolution* 15: evad204. https://doi.org/10.1093/gbe/evad204.

Terbot, J. W., P. Johri, S. W. Liphardt, et al. 2023. "Developing an Appropriate Evolutionary Baseline Model for the Study of SARS-CoV-2 Patient Samples." *PLoS Pathogens* 19: e1011265. https://doi.org/10.1371/journal.ppat.1011265.

Terbot, J. W., V. Soni, C. J. Versoza, M. Milhaven, et al. 2025. "Interpreting Patterns of X Chromosomal Relative to Autosomal Diversity in Aye-Ayes (*Daubentonia madagascariensis*)." *American Journal of Primatology* 87: e70091. https://doi.org/10.1002/ajp.70091.

Terbot, J. W., V. Soni, C. J. Versoza, S. P. Pfeifer, and J. D. Jensen. 2025. "Inferring the Demographic History of Aye-Ayes (*Daubentonia madagascariensis*) From High-Quality, Whole-Genome, Population-Level Data." *Genome Biology and Evolution* 17, no. 1: evae281. https://doi.org/10.1093/gbe/evae281.

Teshima, K. M., G. Coop, and M. Przeworski. 2006. "How Reliable Are Empirical Genomic Scans for Selective Sweeps?" *Genome Research* 16: 702–712. https://doi.org/10.1101/gr.5105206.

The Chimpanzee Sequencing and Analysis Consortium. 2005. "Initial Sequence of the Chimpanzee Genome and Comparison With the Human Genome." *Nature* 437: 69–87. https://www.nature.com/articles/nature04072#group-1.

Thomas, G. W. C., R. J. Wang, J. Nguyen, et al. 2021. "Origins and Long-Term Patterns of Copy-Number Variation in Rhesus Macaques." *Molecular Biology and Evolution* 38, no. 4: 1460–1471. https://doi.org/10.1093/molbev/msaa303.

Thomas, G. W. C., R. J. Wang, A. Puri, et al. 2018. "Reproductive Longevity Predicts Mutation Rates in Primates." *Current Biology* 28, no. 19: 3193–3197.e5. https://doi.org/10.1016/j.cub.2018.08.050.

Thornton, K. R., and J. D. Jensen. 2007. "Controlling the False Positive Rate in Multi-Locus Genome Scans for Selection." *Genetics* 175: 737–750. https://doi.org/10.1534/genetics.106.064642.

Tran, L. A., and S. P. Pfeifer. 2018. *Germ Line Mutation Rates in Old World Monkeys*, 1–10. 1st ed. Wiley. https://doi.org/10.1002/9780470015902.a0028242.

Venn, O., I. Turner, I. Mathieson, N. de Groot, R. Bontrop, and G. McVean. 2014. "Strong Male Bias Drives Germline Mutation in Chimpanzees." *Science* 344, no. 6189: 1272–1275. https://doi.org/10.1126/science.344.6189.1272.

Versoza, C. J., E. E. Ehmke, J. D. Jensen, and S. P. Pfeifer. 2025. "Characterizing the Rates and Patterns of *De Novo* Germline Mutations in the Aye-Aye (*Daubentonia madagascariensis*)." *Molecular Biology and Evolution* 42: msaf034. https://doi.org/10.1093/molbev/msaf034.

Versoza, C. J., J. D. Jensen, and S. P. Pfeifer. 2025. "The Landscape of Structural Variation in Aye-Ayes (*Daubentonia madagascariensis*)." *Genome Biology and Evolution* 17, no. 9: evaf167. https://doi.org/10.1093/gbe/evaf167.

Versoza, C. J., A. Lloret-Villas, J. D. Jensen, and S. P. Pfeifer. 2025. "A Pedigree-Based Map of Crossovers and Noncrossovers in Aye-Ayes (*Daubentonia madagascariensis*)." *Genome Biology and Evolution* 17: evaf072. https://doi.org/10.1093/gbe/evaf072.

Versoza, C. J., and S. P. Pfeifer. 2024. "A Hybrid Genome Assembly of the Endangered Aye-Aye (*Daubentonia madagascariensis*)." *G3: Genes, Genomes, Genetics* 14: jkae185. https://doi.org/10.1093/g3journal/jkae185.

Versoza, C. J., S. Weiss, R. Johal, B. La Rosa, J. D. Jensen, and S. P. Pfeifer. 2024. "Novel Insights Into the Landscape of Crossover and Non-Crossover Events in Rhesus Macaques (*Macaca mulatta*)." *Genome Biology and Evolution* 16, no. 1: evad223. https://doi.org/10.1093/gbe/evad223.

Volampeno, M. S. N., J. C. Masters, and C. T. Downs. 2011. "Home Range Size in the Blue-Eyed Black Lemur (*Eulemur flavifrons*): A Comparison Between Dry and Wet Seasons." *Mammalian Biology* 76: 157–164. https://doi.org/10.1016/j.mambio.2010.04.005.

Wall, J. D., J. A. Robinson, and L. A. Cox. 2022. "High-Resolution Estimates of Crossover and Noncrossover Recombination From a Captive Baboon Colony." *Genome Biology and Evolution* 14, no. 4: evac040. https://doi.org/10.1093/gbe/evac040.

Wang, R. J., Y. Peña-García, M. Raveendran, et al. 2025. "Unprecedented Female Mutation Bias in the Aye-Aye, a Highly Unusual Lemur From Madagascar." *PLoS Biology* 23, no. 2: e3003015. https://doi.org/10.1371/journal.pbio.3003015.

Wang, R. J., G. W. C. Thomas, M. Raveendran, et al. 2020. "Paternal Age in Rhesus Macaques Is Positively Associated With Germline Mutation Accumulation but Not With Measures of Offspring Sociability." *Genome Research* 30, no. 6: 826–834. https://doi.org/10.1101/gr.255174.119.

Williams, A. L., G. Genovese, T. Dyer, et al. 2015. "Non-Crossover Gene Conversions Show Strong GC Bias and Unexpected Clustering in Humans." *eLife* 4: e04637. https://doi.org/10.7554/eLife.04637.

Winn, R. M. 1994. "Preliminary Study of the Sexual Behaviour of Three Aye-Ayes (*Daubentonia madagascariensis*) in Captivity." *Folia Primatologica* 62: 63–73. https://doi.org/10.1159/000156764.

Wong, W. S. W., B. D. Solomon, D. L. Bodian, et al. 2016. "New Observations on Maternal Age Effect on Germline *De Novo* Mutations." *Nature Communications* 7, no. 1: 10486. https://doi.org/10.1038/ncomms10486.

Wu, F. L., A. I. Strand, L. A. Cox, et al. 2020. "A Comparison of Humans and Baboons Suggests Germline Mutation Rates Do Not Track Cell Divisions." *PLoS Biology* 18, no. 8: e3000838. https://doi.org/10.1371/journal.pbio.3000838.

Xue, C., M. Raveendran, R. A. Harris, et al. 2016. "The Population Genomics of Rhesus Macaques (*Macaca mulatta*) Based on Whole-Genome Sequences." *Genome Research* 26, no. 12: 1651–1662. https://doi.org/10.1101/gr.204255.116.

Xue, C., N. Rustagi, X. Liu, et al. 2020. "Reduced Meiotic Recombination in Rhesus Macaques and the Origin of the Human Recombination Landscape." *PLoS One* 15, no. 8: e0236285. https://doi.org/10.1371/journal.pone.0236285.

Yang, Y., M. V. Braga, and M. D. Dean. 2024. "Insertion-Deletion Events Are Depleted in Protein Regions With Predicted Secondary Structure." *Genome Biology and Evolution* 16, no. 5: evae093. https://doi.org/10.1093/gbe/evae093.

Yang, C., Y. Zhou, S. Marcus, et al. 2021. "Evolutionary and Biomedical Insights From a Marmoset Diploid Genome Assembly." *Nature* 594, no. 7862: 227–233. https://doi.org/10.1038/s41586-021-03535-x.

Yoder, A. D. 1997. "Back to the Future: A Synthesis of Strepsirrhine Systematics." *Evolutionary Anthropology: Issues, News, and Reviews* 6, no. 1: 11–22. https://doi.org/10.1002/(SICI)1520-6505(1997)6:1<11::AID-EVAN6>3.0.CO;2-Z.

Zarrei, M., J. R. MacDonald, D. Merico, and S. W. Scherer. 2015. "A Copy Number Variation Map of the Human Genome." *Nature Reviews Genetics* 16, no. 3: 172–183. https://doi.org/10.1038/nrg3871.

Zeng, K. 2013. "A Coalescent Model of Background Selection With Recombination, Demography and Variation in Selection Coefficients." *Heredity* 110: 363–371. https://doi.org/10.1038/hdy.2012.102.

Zhang, R., Y.-Q. Wang, and B. Su. 2008. "Molecular Evolution of a Primate-Specific MicroRNA Family." *Molecular Biology and Evolution* 25, no. 7: 1493–1502.

Zoonomia Consortium. 2020. "A Comparative Genomics Multitool for Scientific Discovery and Conservation." *Nature* 587, no. 7833: 240–245. https://doi.org/10.1038/s41586-020-2876-6.