

# **Title: Local genetic adaptation to habitat in wild chimpanzees**

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5

**Abstract:** How populations adapt to their environment is a fundamental question in biology. Yet  
we know surprisingly little about this process, especially for endangered species such as  
non-human great apes. Chimpanzees, our closest living relatives, are particularly interesting  
because they inhabit diverse habitats, from rainforest to woodland-savannah. Whether genetic  
adaptation facilitates such habitat diversity remains unknown, despite having wide implications  
for evolutionary biology and conservation. Using 828 newly generated exomes from wild  
chimpanzees, we find evidence of fine-scale genetic adaptation to habitat. Notably, adaptation to  
malaria in forest chimpanzees is mediated by the same genes underlying adaptation to malaria in  
humans. This work demonstrates the power of non-invasive samples to reveal genetic  
adaptations in endangered populations and highlights the importance of adaptive genetic  
diversity for chimpanzees.

17

**One-Sentence Summary:** Chimpanzees show evidence of local genetic adaptation to habitat,  
particularly to pathogens, such as malaria, in forests.

20

## 21 Main Text:

Understanding how primates are adapted to their environments provides insights into our own  
evolution and vital information for conservation efforts. This is particularly relevant and urgent  
for our closest living relatives, non-human great apes, all of which are either endangered or  
critically endangered. Chimpanzees (*Pan troglodytes*) have the largest geographic and ecological  
range of any non-human ape (2.6 million km<sup>2</sup> (1)) spanning a variety of environments across  
Equatorial Africa, from dense tropical rainforest to open woodland-savannah mosaics (hereafter  
'savannah' for simplicity (2)). Aside from humans, they are the only great apes that inhabit  
savannah habitats (2). Yet, each of the four subspecies of chimpanzee (central (*P. t. troglodytes*),  
eastern (*P. t. schweinfurthii*), Nigeria-Cameroon (*P. t. ellioti*) and western (*P. t. verus*) (3–5)) are  
endangered (westerns critically so) with numbers continuing to decline due to hunting, habitat  
destruction and infectious diseases (1, 6–8). This decline has widespread negative impacts, as  
chimpanzees are important conservation flagship species for biodiversity protection and crucial  
ecosystem engineers (9–11).

35

Between the forest and savannah extremes, chimpanzees occupy a gradient of habitats known as  
forest-savannah mosaics (12). Forests, which are likely closest to chimpanzee ancestral habitats  
(3, 13), have closed canopies with high availability of food and water throughout the year, and  
therefore tend to support high population densities (2). Forests also harbour a great diversity of  
pathogens and disease vectors (14). Conversely, savannahs are on the edge of chimpanzee

1 distribution in East and West Africa and are characterised by open canopies, higher temperatures,  
2 lower annual rainfall and higher rainfall seasonality (2, 15).

3

4 The occupation of such a range of habitats is facilitated by chimpanzee behavioural diversity  
5 (16). Savannah chimpanzees exhibit unique thermoregulatory behaviours (17, 18) and on  
6 average trend towards greater behavioural diversity than forest chimpanzees (16)—a potential  
7 adaptation to higher environmental variability. Behavioural adaptations also include tool use in a  
8 range of contexts such as foraging (19–21), water extraction (22–24) and communication (25).  
9 Nevertheless, behaviour does not fully compensate for stressors, as shown by physiological  
10 stress in response to pathogens (26–29) and environmental pressures (15, 30). Another  
11 mechanism that can facilitate the occupation of diverse habitats is genetic adaptation, just as  
12 local adaptation has contributed to genetic population differentiation in humans (31) despite  
13 great behavioural flexibility (32, 33). In fact, humans have evolved local genetic adaptations to  
14 environmental pressures that differ between forest and savannah habitats, including pathogens  
15 (34–36) such as malaria (37, 38), and climatic variables such as temperature and water  
16 availability (39, 40), diet (41–43), and solar exposure (44). Culture can also promote genetic  
17 adaptations, such as in human adaptations to diet and zoonotic diseases associated with animal  
18 domestication (43, 45).

19

20 Establishing if genetic differences underlie local adaptation in chimpanzees is important to  
21 understanding primate evolution and critical for chimpanzee conservation. If adaptive genetic  
22 differences exist among populations, this genetic diversity must be conserved to maintain  
23 existing adaptations and adaptive potential (46, 47). Additionally, recent genetic adaptations  
24 highlight key selective pressures that likely shape fitness in the wild today, and can help establish  
25 which populations may be more vulnerable to environmental change (46). This is particularly  
26 relevant in the face of anthropogenic climate change, which is increasing temperatures and  
27 precipitation seasonality within the chimpanzees' range (2). Furthermore, chimpanzees are  
28 excellent models for understanding our own evolution, particularly in savannah regions, which  
29 resemble early hominin habitats (2, 48–52). Lastly, the close genetic similarity between humans  
30 and other great apes (53) has resulted in zoonotic disease transmissions (54, 55) such as  
31 HIV-1/AIDS (56) and malaria (57). Understanding how chimpanzees have evolved to reduce the  
32 pathogenicity of microorganisms can thus reveal potential targets for treatments and vaccines  
33 (58–61).

34

35 We have a growing understanding of chimpanzee demographic history thanks to population  
36 genomics studies (3, 5, 62), which have identified genetic differentiation among populations  
37 within each subspecies. However, our knowledge of genetic adaptation lags behind, largely due  
38 to sample limitations. Because existing genomic datasets include only dozens of captive  
39 chimpanzees of unknown geographic origin (5, 62–64), previous studies investigated adaptation  
40 only at the subspecies level (63, 65–73), revealing interesting subspecies-level adaptations e.g.,

1 to pathogens such as SIV (65, 66). However, habitats vary greatly within chimpanzee subspecies  
2 ranges (12); therefore, subspecies comparisons are uninformative on adaptations to many  
3 potential selective pressures. Investigation of fine-scale local adaptation is essential for  
4 understanding adaptation in chimpanzees but requires large numbers of DNA samples from wild  
5 individuals of known geographic origin, coupled with detailed environmental data.

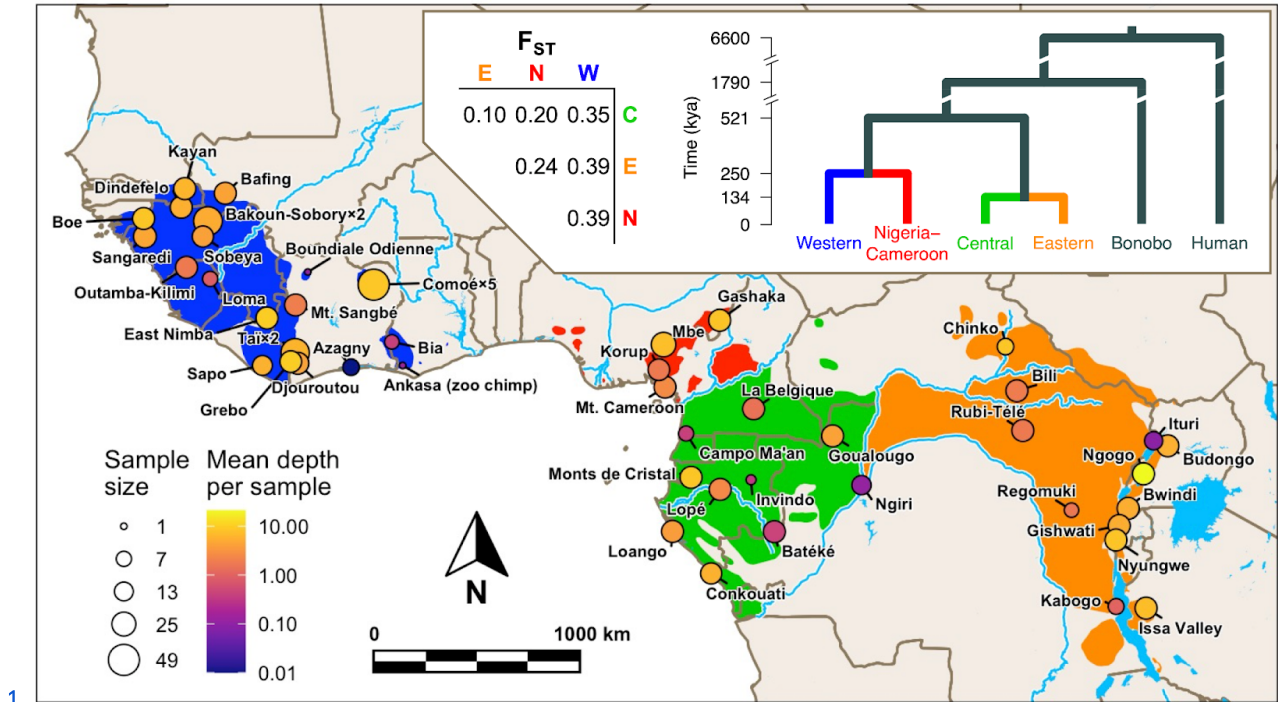
6  
7 Non-invasive sampling is the only ethical and feasible option for studying wild populations of  
8 many protected species (74), including non-human apes; however, recent technical and analytical  
9 advancements are beginning to enable population genomic analyses on such samples (3, 75–80).  
10 Using faecal samples from wild individuals collected as part of the Pan African Programme: The  
11 Cultured Chimpanzee (PanAf) (3, 81), we have generated full exome (protein-coding regions of  
12 the genome) sequences from hundreds of chimpanzees across their geographic and  
13 environmental range. We demonstrate that genomic data from non-invasive samples can be used  
14 to reveal the fine-scale adaptive history of endangered primates. Specifically, when integrated  
15 with environmental data, the exomes reveal evidence of local genetic adaptation to habitat  
16 conditions in chimpanzees. In forests, we find evidence of pathogen-mediated adaptation,  
17 including to malaria via the same loci that mediate malaria adaptation in humans.

## 18 Samples and sequences

19 Faecal samples of 828 unique individuals were collected from 52 sampling sites across the  
20 geographic range of all four chimpanzee subspecies as part of PanAf (3, 81). This represents a  
21 ten-fold increase in sample size and a massive increase in geographic coverage over existing  
22 genome-wide datasets (5, 62) of any non-human ape. The scale and resolution of the dataset are  
23 only comparable to the chromosome 21 (chr21) sequences of the same individuals (3).

24  
25 Non-invasive samples typically contain low levels of endogenous DNA. Thus, we  
26 target-captured and sequenced full exomes (akin to chr21 (3)) because they are informative for  
27 the vast majority of functional sites in the genome, including both sequenced protein-coding and  
28 linked regulatory regions (e.g., promoters). Samples were strictly filtered to omit those with  
29 first-order relatives, contamination or low read depth (Supplemental Note 3). To mitigate the  
30 potential effects of the moderate read depth and take advantage of the large sample size, we used  
31 genotype likelihoods and allele frequency-based methods, which minimised the effects of  
32 individual sequencing errors.

33



**Fig. 1. Chimpanzee exome dataset distribution, sample size and coverage.** Top panel: Hominini phylogenetic tree highlighting chimpanzee subspecies with estimated evolutionary split times (62, 82) (thousands of years ago (kya)) and pairwise  $F_{ST}$  between subspecies (65). Main panel: map of West, Central and East Africa indicating the location of sample sites, sample sizes and mean exome sequencing read depth per sample. Each point represents a sample site except for five geographically close sites sampled at Comoé, two at Taï and two at Bakoun-Sobory. The geographic distribution of each subspecies is shown (green=central, orange=eastern, red=Nigeria-Cameroon, blue=western) (I) with major rivers and lakes indicated in light blue. The sample sizes and populations in the final filtered dataset used for selection analyses are shown in Fig. 3.

As expected, using either exomes or chr21 (3), population structure analyses separate samples into four subspecies (Figs. S12, S14 and S15), and within-subspecies population structure inferred with the exomes closely matches results from chr21 (3) (Figs. S12-16). Each sample site was considered a genetic unit, which we refer to as a ‘population’, except for four populations formed by combining very closely related sample sites (details in Materials and Methods and Supplemental Note 4). After removing populations with fewer than eight samples, the final dataset contains 388 exomes (385 chr21) from 30 populations: 5 central, 9 eastern, 2 Nigeria-Cameroon and 14 western. The resulting exomes have a median read depth per sample of 5.30-fold (0.51- to 52.27-fold) in the exome target space (60Mbp). The signatures of local adaptation within and across subspecies were investigated in four ‘subspecies-datasets’ containing populations from all subspecies (All), central and eastern together (Central-Eastern), Nigeria-Cameroon (Nigeria-Cameroon) and western (Western). Central and eastern were

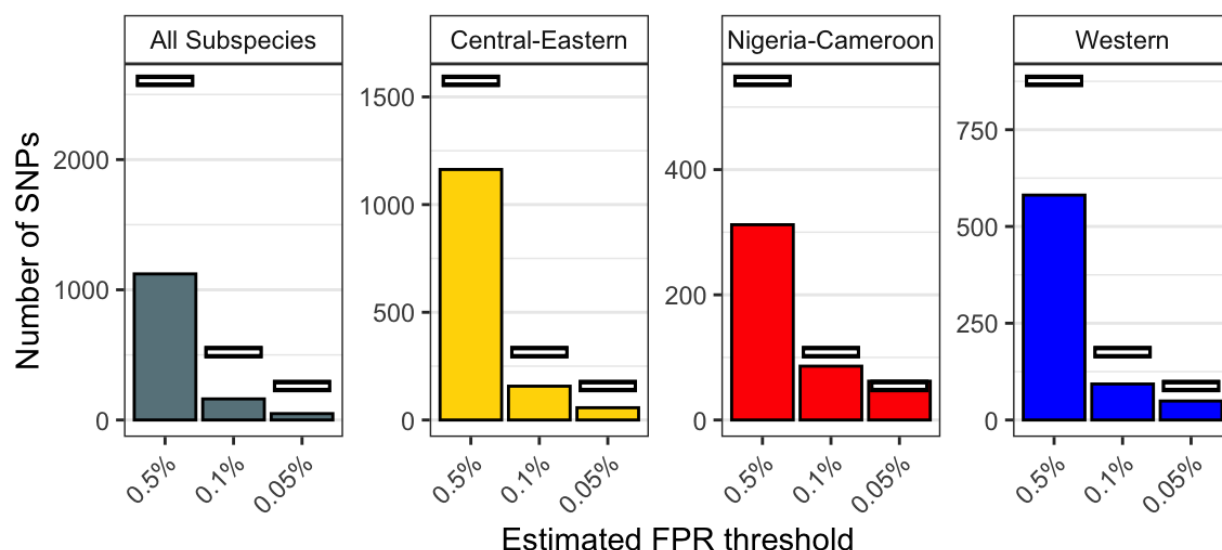
1 combined because of their low genetic differentiation ( $F_{ST}=0.10$ , Fig. 1) (65). The unfolded site  
2 frequency spectra (SFS) conform to expectations given the inferred demographic history of these  
3 subspecies (Fig. S18).

#### 4 Allele frequency population differentiation

5 Local adaptation increases the frequency of alleles only where they are beneficial, generating  
6 large allele frequency differences among populations. We first investigated local positive  
7 selection by analysing population differentiation with a genetics-only hypothesis-free analysis  
8 using the BayPass (83) core model. BayPass estimates the genome-wide population allele  
9 frequency covariance matrix, which is used to standardise allele frequencies for each  
10 single-nucleotide polymorphism (SNP) with respect to population structure (BayPass effectively  
11 accounts for population structure here, see Supplemental Note 4); the variance across  
12 populations of these standardised frequencies is summarised in the test statistic  $X'X^*$  (84). SNPs  
13 under local adaptation are expected to have exceptionally large population allele frequency  
14 differentiation, and therefore the highest  $X'X^*$  values in the genome. Null expectations under  
15 neutrality were generated using the non-genic regions of chr21 (non-genic-chr21) in these  
16 samples (3). Generating an empirical null frees the analysis from demographic assumptions and  
17 accounts for many potential confounding factors because non-genic-chr21 has an almost  
18 identical demographic history, sample size and read depth to the exome and has been processed  
19 in the exact same way (Supplemental Note 6.2). Candidate targets of positive selection (hereafter  
20 ‘candidate SNPs’) were defined as the exome SNPs with higher  $X'X^*$  than the values  
21 corresponding to estimated false positive rates (FPR) of 0.5%, 0.1% and 0.05% using the  
22 non-genic-chr21  $X'X^*$  distribution while accounting for read depth (details in Materials and  
23 Methods and Supplementary Note 6.3.2).

24  
25 If local adaptation drives population differentiation, we expect exomes to show an excess of  
26 highly differentiated SNPs compared to neutral expectations. Contrary to this expectation, there  
27 are fewer SNPs with very large  $X'X^*$  values in the exome compared to null expectations (Fig. 2,  
28 Fig. S27), potentially reflecting the effects of purifying selection in the exome. It remains  
29 possible that specific selection pressures have driven local genetic adaptation in chimpanzees but  
30 we do not observe evidence of this at the genome level using exomes alone.

31



1

2 **Fig. 2. Number of genetics-only candidate SNPs.** The number of candidate SNPs from the  
3 genetics-only test (bars) compared to the null expectation (white lines) at  $X^*X^*$  thresholds  
4 corresponding to estimated FPRs of 0.5%, 0.1% and 0.05%, for each subspecies-dataset. Note  
5 that y-axis scales are not consistent across panels.

## 6 Genetic adaptation to habitat

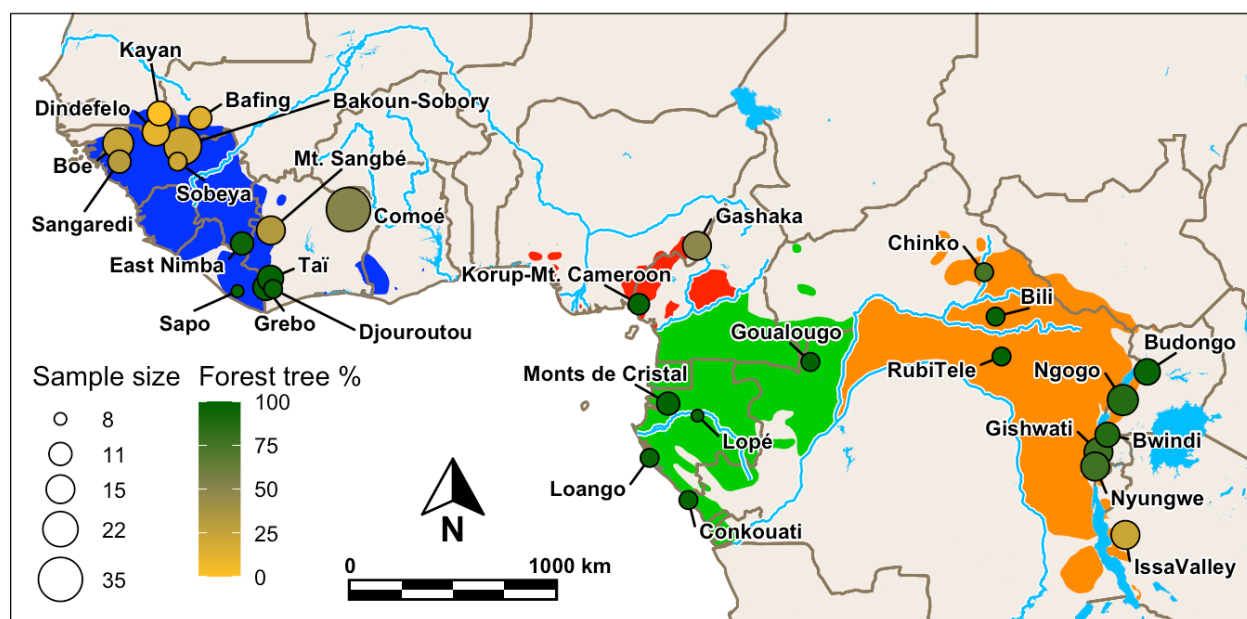
7 Integrating genetic and environmental data increases the power to detect signatures of local  
8 adaptation (85, 86) and allows us to directly test the hypothesis that chimpanzees have adapted to  
9 selection pressures that vary between habitats. We thus performed a genotype-environment  
10 association (GEA) test by integrating an environmental covariable into the analysis using the  
11 BayPass AUX model (83). BayPass calculates a Bayes factor (BF) for each SNP that indicates  
12 the strength of evidence for the linear correlation between population allele frequencies and the  
13 environmental covariable while accounting for population structure (Supplemental Note 6.4.5).  
14 SNPs evolving under local adaptation are expected to be highly correlated with the relevant  
15 environmental covariable and therefore have the highest BF in the genome.

16

17 Environmental metrics based on temperature, precipitation or land cover do not correspond well  
18 with researcher-defined forest and savannah regions (12). Therefore, we used a floristic measure  
19 informed by a large-scale biogeographic analysis which identified very different tree species  
20 compositions between forest and savannah regions and has been shown to produce more accurate  
21 maps of habitat distributions across Africa (87). Specifically, we used the percentage of trees  
22 identified as ‘forest specialists’ (87) among all the classified trees recorded at each sample site  
23 (hereafter ‘forest-tree-percentage’) (Fig. 3) (see Materials and Methods and Supplemental Note 2  
24 for details). This variable is ideal because the data was collected within the known ranges of the  
25 sampled populations and the same field protocol can be applied to new sample sites, making our

1 data and results comparable to future studies incorporating additional sample sites. This variable  
2 is not used here to test for adaptation to tree species compositions *per se*; rather, it is used to  
3 describe the chimpanzee habitat gradient, which summarises many potential selective pressures.  
4 The GEA analysis was run with this covariable in each subspecies-dataset except  
5 *Nigeria-Cameroon*, as it has only two populations. Candidate SNPs were selected as in the  
6 genetics-only test (details in Supplementary Note 6.4.1).

7



8

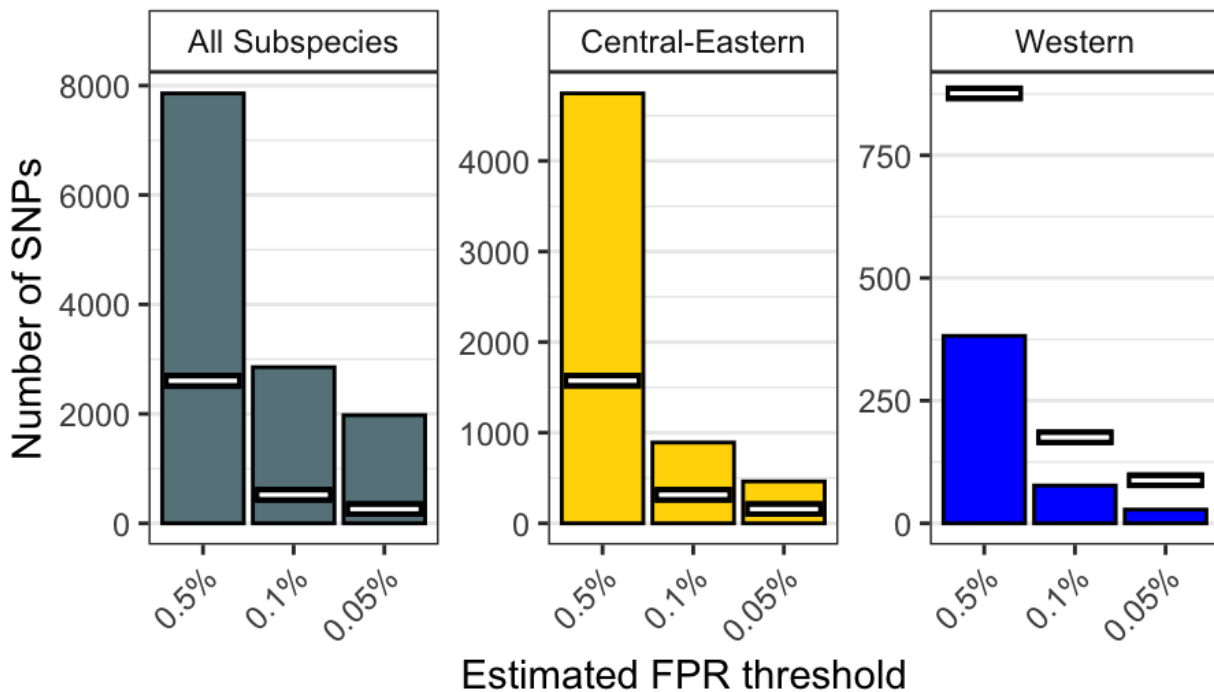
9 **Fig. 3. BayPass analysis dataset.** Map of West, Central and East Africa showing the location,  
10 sample size (after filtering) and forest-tree-percentage for each population in the BayPass  
11 analyses. The ranges of the four subspecies are shown (green=central, orange=eastern,  
12 red=Nigeria-Cameroon, blue=western) (1) with major rivers and lakes indicated in light blue.

13

14 In contrast to the genetics-only results, the GEA shows a substantial excess of SNPs strongly  
15 associated with forest-tree-percentage in the exome when compared with neutral expectations in  
16 *All* and *Central-Eastern* (Fig. 4). This excess is what we expect under local adaptation associated  
17 with habitat. This excess is not present in *Western*, as expected if the strong population  
18 bottleneck experienced by this subspecies (3, 5, 62) increased drift and reduced the efficacy of  
19 natural selection, or if recent gene flow (3) inhibited the evolution of local adaptation (Fig. 4).  
20 Nevertheless, this does not exclude the possibility that strong selective forces may have driven  
21 local adaptation in the western subspecies, and the SNPs with the highest BF<sub>s</sub> in the exome are  
22 the best candidate targets of positive selection. Read depth and population substructure do not  
23 drive our candidates, and independent tests confirm that candidate allele frequencies correlate  
24 strongly with forest-tree-percentage (Figs. S39 and S44-46). For all thresholds and  
25 subspecies-datasets, the minimum BF is very high: over 14.7 for FPR<0.5%, over 18.3 for  
26 FPR<0.1% and over 19.5 for FPR<0.05% (Fig. S38). Jeffrey's rule (88) defines 15<BF<20 as

1 ‘very strong evidence’ and  $BF > 20$  as ‘decisive evidence’, demonstrating that a vast majority of  
2 candidate SNPs have very strong evidence of being associated with habitat, with almost all SNPs  
3 in the 0.1% tail having decisive evidence (Fig. S37).

4  
5 These results provide strong evidence for local genetic adaptation to habitat in chimpanzees,  
6 revealing the presence of important genetic differences among wild populations, even within  
7 subspecies, that likely shape fitness in an environment-dependent way.

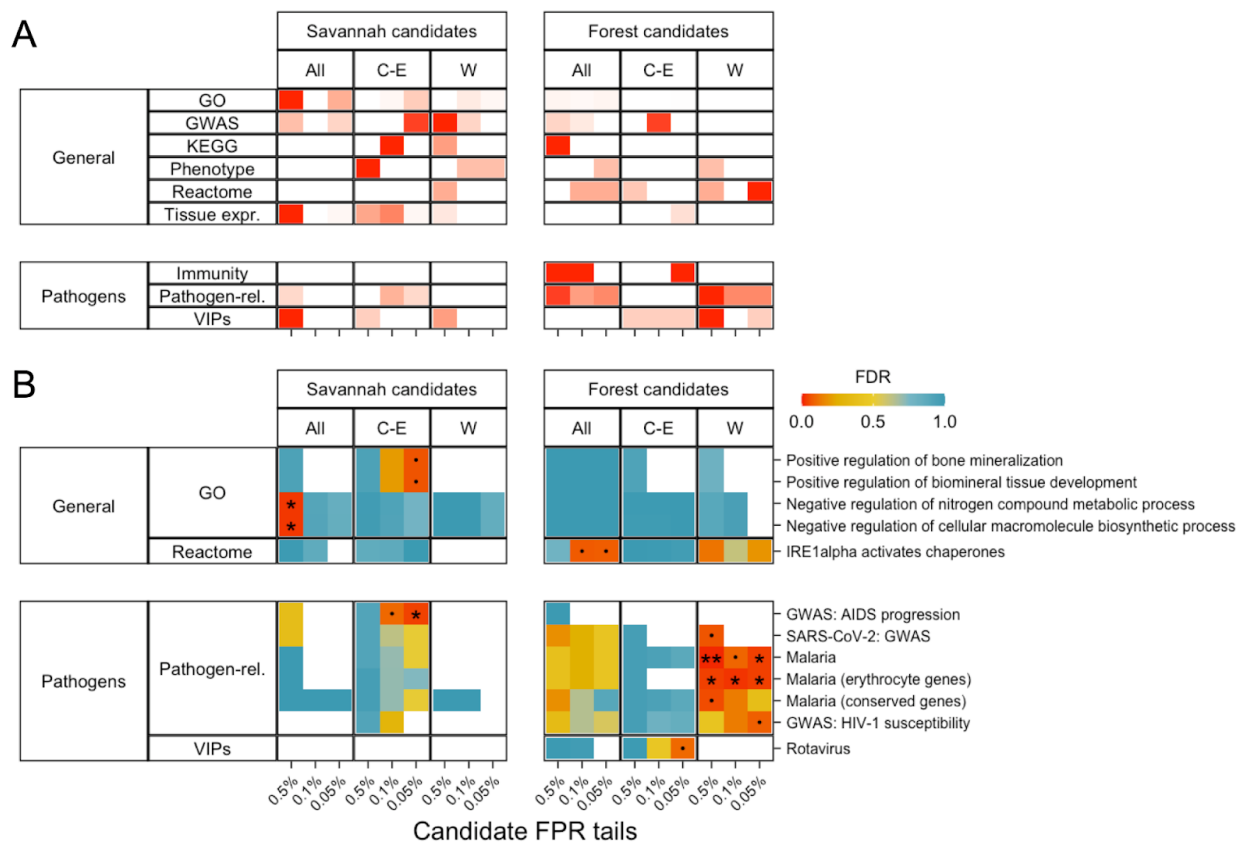


8  
9 **Fig. 4. Number of GEA candidate SNPs.** The number of candidate SNPs from the GEA (bars)  
10 compared to the null expectation (white lines) at BF thresholds corresponding to estimated FPRs  
11 of 0.5%, 0.1% and 0.05%, for each subspecies-dataset tested. Note that y-axis scales are not  
12 consistent across panels.

13  
14 Under the reasonable assumption that novel adaptations are more commonly mediated by the  
15 novel, derived allele than the ancestral one, we assigned SNPs as associated with forest or  
16 savannah adaptations according to the sign of their correlation coefficient. There is an excess of  
17 SNPs with high BF<sub>s</sub> in the exome for both savannah and forest candidates (Fig. S42) in *All* and  
18 *Central-Eastern*, suggesting that adaptation in either direction contributes to the overall excess.  
19 To interpret these loci biologically, we investigated the genes the candidate SNPs fall within  
20 (hereafter ‘candidate genes’) by testing for an overrepresentation of functional categories in  
21 hypothesis-free gene set enrichment analyses. Given the relevance of pathogens as selective  
22 pressures (65, 66), we also performed a hypothesis-driven enrichment analysis of

1 pathogen-related genes (details in Supplemental Note 7). Interestingly, these analyses point to  
2 potential differential adaptations in savannah and forest chimpanzees.

3



4

5 **Fig. 5. GEA candidate gene set enrichment results.** Results for 0.5%, 0.1% and 0.05% FPR  
6 tails for savannah and forest candidate SNPs are shown. Vertical panels indicate results from  
7 each subspecies-dataset. Horizontal panels show the broad categories that the gene sets belong  
8 to. Multiple testing correction was done within each gene set enrichment analysis run (i.e., each  
9 tail and gene set database such as ‘Pathogen-related’, ‘GWAS’, ‘Phenotype’ etc.). (A) the  
10 number of gene sets with FDR<0.5, cells are coloured in a gradient from white (0) to red (the  
11 largest value per row) (Fig. S50 shows the numbers in each cell). (B) shows the FDR values for  
12 the most enriched gene sets with FDR<0.1 for at least one candidate tail in at least one  
13 subspecies-dataset (‘.’ FDR<0.1, ‘\*’ FDR<0.05, ‘\*\*’ FDR<0.01).

#### 14 *Adaptations to savannah*

15 Savannah candidate genes belong to many categories associated with physiological traits when  
16 compared to forest candidate genes (Fig. 5A). There are over six times more “General” gene  
17 categories with an FDR<0.5 in savannah than forest candidates (260 vs 42, Figs. 5A and S50),  
18 although only two of these categories are significantly enriched (FDR < 0.05) (Fig. 5B) (negative  
19 regulation of nitrogen compound metabolic processes and negative regulation of cellular  
20 macromolecule biosynthetic processes). This would be compatible with a large degree of

1 polygenicity in the genetic adaptation of chimpanzees to the environmental extremes of  
2 savannahs. The diversity of categories and their overlap in genes makes it difficult to infer  
3 selection pressures that may drive this signal.

4

5 Restricted availability of water in savannahs during the dry season is a potential selection  
6 pressure (17, 30) that could partially explain the enrichment of physiological categories in our  
7 candidates. Nevertheless, there is no significant enrichment in the two dehydration response gene  
8 categories we analysed (89, 90) (Supplemental Note 7), neither in the GEA nor genetics-only  
9 candidates (Fig. S51). Chimpanzees may thus have adapted to dehydration stress through genes  
10 not included in these categories or through behavioural adaptations (e.g., well digging (22)).  
11 Alternatively, dehydration stress may be present but independent of habitat (15).

12

13 There is limited evidence of adaptation to pathogens in savannah populations (Fig. 5A, left  
14 bottom corner). Savannah candidates are significantly enriched ( $FDR < 0.05$ ) for only one  
15 pathogen-related gene set: genes associated with AIDS progression in GWAS at the  
16 *Central-Eastern* 0.05% tail (Fig. 5B), which contains only two candidate genes (Table S2).  
17 Viruses similar to SIV/HIV are not known to be associated with savannahs, instead, this result  
18 may be explained by adaptation in Issa Valley, which has a high prevalence of SIV (91, 92) and a  
19 particularly low forest-tree-percentage in *Central-Eastern* (Fig. 3). Being extreme in  
20 forest-tree-percentage means that Issa Valley weighs heavily on the *Central-Eastern* savannah  
21 candidates, although without fully driving them (Supplemental Note: 6.4.6). Analysis of  
22 additional populations will help establish to what extent the evidence of adaptation is general  
23 across central and eastern savannah populations, and identify the specific adaptive mechanisms  
24 and selective factors. In any case, the excess of exonic savannah candidate SNPs in *All* and  
25 *Central-Eastern* suggests that chimpanzees do harbour genetic adaptations to savannah habitats.

## 26 *Adaptations to forest*

27 While forest candidates show weak enrichment in general physiological categories, they show a  
28 pattern of stronger enrichment in pathogen-related genes as shown in stronger enrichment for  
29 general “immunity genes” (93) and “innate immunity genes” (94) in the forest than savannah  
30 candidates in *All* and *Central-Eastern* (Fig. 5A). This pattern is also evident for individual  
31 pathogen categories in *All* and especially in *Western*, although not in *Central-Eastern* (Fig. 5).  
32 This is consistent with the higher population densities (2) and increased pathogen exposure (14)  
33 in forests resulting in a greater infectious disease burden. In humans, local adaptation has likely  
34 also been driven by high pathogen diversity (95), particularly in tropical forests (34–36).  
35 *Central-Eastern* does not show this pattern, likely due to the presence of eastern populations  
36 from montane forests, which are considerably cooler than lowland forests and therefore have  
37 lower levels of vector-borne diseases such as malaria (14) (Supplemental Note 7.2.1).  
38 Enrichment of pathogen-related categories in the *Western* forest candidates suggests that,

1 although we do not see evidence of positive selection on the genome-scale, strong selection at a  
2 limited number of pathogen-related genes is likely driving local adaptation in this subspecies.

3

4 Focusing on individual pathogens, the strongest and clearest signal is enrichment for  
5 malaria-related categories in *Western* forest candidates (Fig. 5B, Table S2). They are  
6 significantly enriched (FDR<0.05) in “Malaria related genes” (96) at the 0.5% and 0.05% tails  
7 and “Erythrocyte genes related to malaria” (97) at all three tails; enrichment in  
8 *Plasmodium*-interacting proteins that are conserved across mammals (98) (thus excluding  
9 haemoglobin and glycophorin genes, see below) very narrowly exceeds the significance  
10 threshold (FDR=0.050) in the 0.5% tail. Interestingly, malaria infection probability in  
11 chimpanzees is closely correlated with canopy cover (14), which is itself highly correlated with  
12 forest-tree-percentage in our dataset (Pearson  $r = 0.92$ ,  $p = 9.044 \times 10^{-13}$ ) (99). Malaria is a major  
13 selection pressure and has driven some of the clearest examples of local adaptation in humans  
14 (37, 38). Only five genetic variants have been significantly associated with severe malaria in  
15 human GWAS (100, 101). Strikingly, two of these loci, which encode for haemoglobin (HB) and  
16 glycophorin (GYP) genes (Fig. 6A), contain chimpanzee forest candidate SNPs; both of which  
17 also underlie adaptations to malaria in humans (102–105).

18

19 For HB, candidate SNP chr11:5254366 (*Western* 0.5% and *All* 0.05% tails) lies within an intron  
20 of Haemoglobin Subunit Delta (*HBD*), less than 5kb upstream of the adjacent paralogue  
21 Haemoglobin Subunit Beta (*HBB*). While mutations in *HBD* have little effect on malaria  
22 resistance due to low expression in adults (106), the HbS mutation in *HBB* is a classic example  
23 of balancing selection in humans, as heterozygotes are protected against severe malaria (102,  
24 103). Therefore, the signatures that we observe may reflect selection on a linked variant within  
25 *HBB*, the regulation of *HBB* or *HBD* itself. In any case, it is striking that this locus shows  
26 evidence of local adaptation in both chimpanzees and humans.

27

28 For GYP, two candidate SNPs, chr4:145040845 and chr4:145039806 (*Western* 0.5% and 0.05%  
29 tails respectively) lie within Glycophorin A (*GYP A*) (Ensemble hg19 also places them within an  
30 intron of Glycophorin B (*GYP B*) likely due to an annotation error, see Supplemental Note 8.2)  
31 (Fig. S52). The evidence for selection at this locus is strong with chr4:145039806 having the 23<sup>rd</sup>  
32 highest BF in *Western* accounting for read depth ( $FPR \leq 2.91 \times 10^{-4}$ ). In *All*, there are six forest  
33 candidate SNPs in *GYP A* including chr4:145040845 (0.05% tail) and chr4:145039806 (0.5%  
34 tail), and another *GYP A* SNP is a candidate in the genetics-only 0.5% tail (Fig. S52).

35

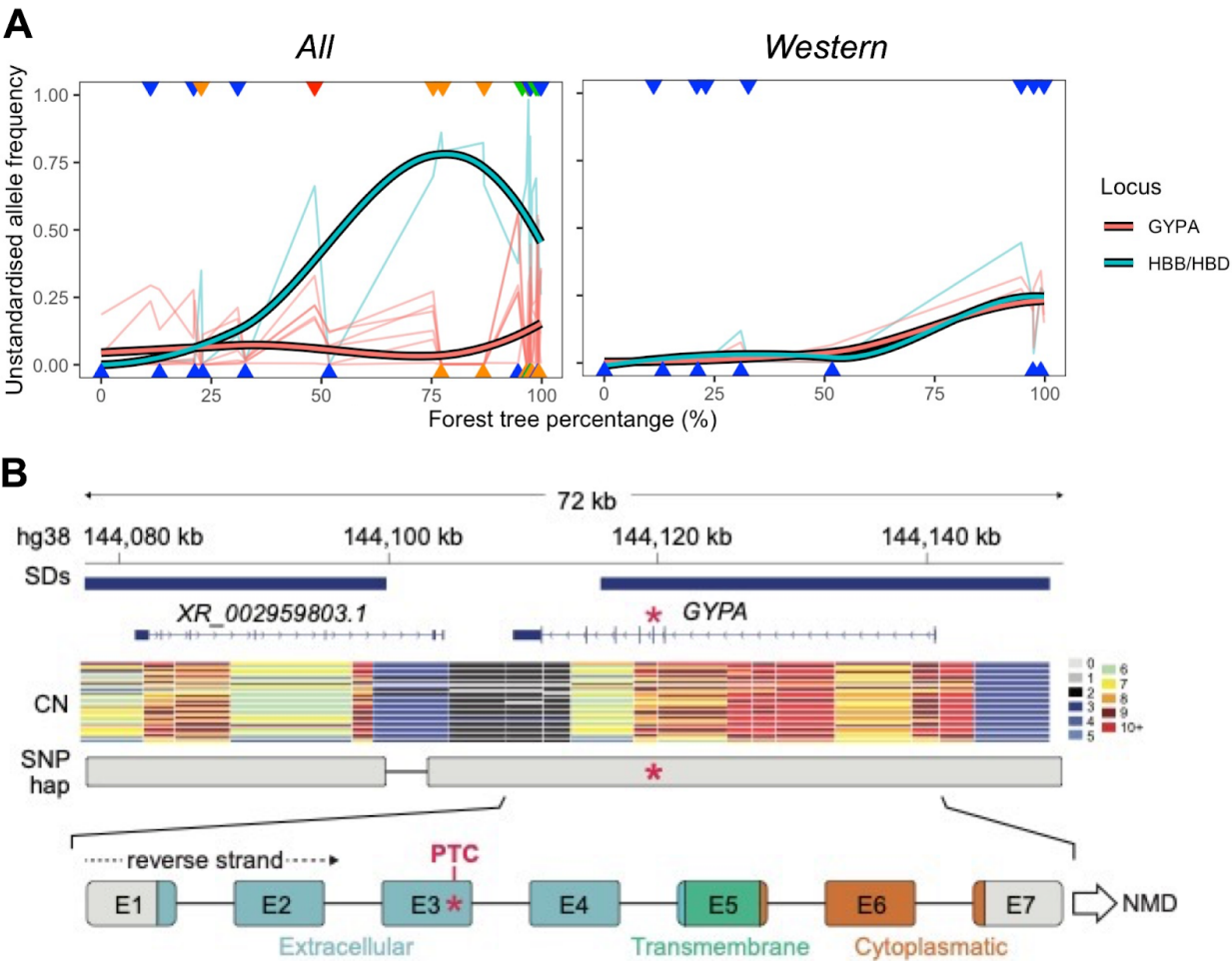
36 *GYP A* and *GYP B* encode glycophorins used by *Plasmodium falciparum* to enter erythrocytes  
37 (107). In humans, structural variants associated with this locus appear to mediate adaptation to  
38 malaria (104, 105, 108–112). It is therefore interesting to investigate structural variation in  
39 chimpanzees. Read depth in the PanAf exomes is not unusual at this locus, but low-coverage  
40 target capture data is not ideal for investigating structural variation. Copy-number (CN) estimates

1 from high-coverage short-read (n=60) (5, 62) and long-read data (n=2) (113, 114) from captive  
2 chimpanzees confirm that, in addition to the full-length and likely ancestral *GYP A*, chimpanzees  
3 also carry 2–9 copies of truncated paralogues lacking the last two exons of *GYP A*, which encode  
4 for the cytoplasmic domain (115) (Supplemental Note 8.1, Fig. 6B, Fig. S53D). Thus, like in  
5 humans, structural variants contribute to the complexity of the locus in chimpanzees. We note  
6 that the *GYP A* candidate SNPs are present in both the long-read (113, 114) and high-coverage  
7 short-read (5, 62) data (Fig. S55), confirming them to be true polymorphisms; further, there is no  
8 evidence of an association between forest-tree-percentage and read-depth in the PanAf exomes at  
9 these SNPs (Fig. S54, details in Supplemental Note 8.1).

10

11 The long-read data (113, 114) show the *GYP A* candidate SNPs residing in a single haplotype  
12 spanning the full-length gene (Fig. 6B, Fig. S53C). The candidate allele at chr4:145040845  
13 introduces a premature stop gain in exon 3 of *GYP A* (E76X) predicted to result in degradation of  
14 the mRNA by nonsense-mediated decay (116); even if the truncated protein was translated, it  
15 would encode only a partial extracellular domain and be missing the remaining extracellular and  
16 entire transmembrane and cytoplasmic domains (115), resulting in non-functional *GYP A*. Thus,  
17 as suggested for *GYP A* deletions in humans (109), this SNP may be the target of natural  
18 selection, by preventing the expression of a key receptor protein used by the malaria parasite to  
19 enter erythrocytes (107).

20



**Fig. 6. Key malaria-related forest candidate genes.** (A) Derived allele frequencies of candidate SNPs at the *HBB/HBD* (green) and *GYP A* (red) loci plotted against forest-tree-percentage, with population values indicated with triangles coloured according to subspecies (green=central, orange=eastern, red=Nigeria-Cameroon, blue=western) arbitrarily assigned to the top or bottom of the graph to reduce overlap. Left for candidate SNPs and populations from *All*. Right for candidate SNPs and populations from *Western*. Thin lines represent the estimated population allele frequencies for each candidate SNP, thick lines show the smoothed pattern of all candidate SNPs per locus using LOESS. (B) Diagram of the *GYP A* locus in hg38 coordinates, including segmental duplications (SDs), copy numbers (CN) across captive chimpanzees, representative long-read sequencing haplotype containing candidate SNP C>A at chr4:145040845 in hg19 coordinates (red asterisk), and schematic representation of the candidate SNP location within *GYP A* exons (E1-7). PTC: premature termination codon. NMD: Nonsense-mediated mRNA decay. The PTC SNP is 210 exonic base pairs upstream of the last exon-exon junction (between exons 6 and 7), and therefore, likely to cause NMD according to the 50–55nt rule (116).

## Conclusions

We present the largest population genomic study of natural selection in a non-human ape to date,

1 capturing and sequencing the exome from non-invasive samples of hundreds of wild  
2 chimpanzees and integrating these exomes with previously published full chr21 sequences from  
3 the same samples (3). Even in the face of limitations from non-invasive sampling (Supplemental  
4 Note 1), this work demonstrates that population genomics can reveal the presence of local  
5 genetic adaptation in an endangered species.

6

7 The genotype-environment association analysis provides strong, genome-scale evidence of local  
8 adaptation to habitat in *All* and *Central-Eastern*—although not in *Western*, likely because of their  
9 small long-term  $N_e$  (5, 62). This demonstrates the power of genotype-environment associations  
10 (GEA) to identify positive selection by revealing signatures of local adaptation in the form of  
11 subtle allele frequency changes correlating with a relevant covariable (Supplemental Note 6.4.4).  
12 Indeed, the GEA candidate SNPs differ consistently in allele frequency with respect to habitat  
13 but generally do not have large frequency differences between populations (Fig. S45A). This is  
14 consistent with local adaptation in chimpanzees being mostly polygenic and driven by soft  
15 sweeps as observed in humans (32, 117, 118), and suggests the presence of complex genetic  
16 adaptations even in the absence of fixed differences among populations.

17

18 Our findings suggest that while behaviours such as tool use (16, 119) and thermoregulatory  
19 behaviours (17) are important in mitigating environmental stressors, selective pressures  
20 associated with habitat still appear to drive genetic adaptation in chimpanzees. Thus, both  
21 behavioural flexibility and genetic adaptation may explain how chimpanzees inhabit such a range  
22 of habitats. Far from replacing genetic adaptation, behavioural adaptations may drive genetic  
23 changes via gene-culture coevolution (120), as seen with human diets (43), whereby behavioural  
24 flexibility facilitates exposure to novel selection pressures that later drive genetic adaptations.

25

26 The evidence of genetic adaptation in forests demonstrates the importance of novel adaptations  
27 even in habitats with high availability of resources that support high population densities. This is  
28 perhaps because the struggle against the high pathogen load of lowland forests shapes the  
29 evolution of these populations. This is not surprising, as pathogens have been important selective  
30 pressures for chimpanzees over longer time scales (65, 66). Today, infectious diseases are major  
31 causes of chimpanzee population decline(1) and recent increased exposure to humans has led to  
32 an increase in deadly outbreaks caused by cross-species transmission (121). Our findings  
33 highlight the importance of genetic adaptation in shaping infectious disease mortality in  
34 chimpanzees and suggest that individuals are adapted to the pathogens present in their local  
35 habitat, emphasising the dangers of displacement and environmental change.

36

37 Evidence of adaptation to malaria in forests is particularly interesting. A range of malaria  
38 parasites infect wild chimpanzees, including three *Laverania* species closely related to *P.*  
39 *falciparum*, which originated in gorillas (57, 122) and is now responsible for 90% of global  
40 malaria mortality in humans (123). However, the fitness effects of malaria in wild chimpanzees

1 are poorly understood (124). Its high prevalence in wild populations (122) and the few studies of  
2 captive chimpanzees suggest that severe effects are rare (125–128). However, fitness effects in  
3 the wild may be more severe than in captivity, as demonstrated by the largely asymptomatic SIV  
4 infections in captivity (58, 129, 130) but fitness effects in the wild (29, 131). Young chimpanzees  
5 and pregnant mothers are particularly susceptible to malaria infection (132, 133), which may  
6 lead to higher morbidity/mortality as observed in humans (134). Our findings indicate that  
7 malaria has been an important selection pressure in the recent past and may have important  
8 fitness effects in present-day wild populations. That adaptation appears to be mediated by the  
9 same few genes in chimpanzees and humans is striking from an evolutionary point of view;  
10 further, it demonstrates how understanding chimpanzee evolution can inform human medicine.

11  
12 Chimpanzees also appear to have adapted genetically to savannah habitats, although identifying  
13 key selective pressures and adaptive traits is harder. Studying additional savannah populations  
14 would help address this question. This would provide insights into how our ancestors may have  
15 adapted to similar habitats, and have important implications for the conservation of wild  
16 chimpanzees as their habitats become hotter and more seasonal under climate change (2).

17  
18 Just as previous studies highlighted the importance of conserving behavioural diversity (16, 135,  
19 136), we emphasise the importance of conserving adaptive genetic diversity across chimpanzees’  
20 ecological range to maintain their adaptive potential and ensure long-term survival in the wild  
21 (46, 74). This is important because chimpanzee habitats are changing rapidly due to direct  
22 anthropogenic destruction (1, 137, 138), climate change (139) and disease transmission (121,  
23 140). We emphasise the need to protect all chimpanzee habitats and to consider local genetic  
24 adaptations when planning conservation efforts to ensure that individuals are adapted to the local  
25 environment. Finally, our study demonstrates the value and promise of non-invasive sampling to  
26 investigate genetic adaptation in endangered species.

27

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