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Extreme selective sweeps independently targeted the X chromosomes of the great apes

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The unique inheritance pattern of the X chromosome exposes it to natural selection in a way that is different from that of the autosomes, potentially resulting in accelerated evolution. We perform a comparative analysis of X chromosome polymorphism in 10 great ape species, including humans. In most species, we identify striking megabase-wide regions, where nucleotide diversity is less than 20% of the chromosomal average. Such regions are found exclusively on the X chromosome. The regions overlap partially among species, suggesting that the underlying targets are partly shared among species. The regions have higher proportions of singleton SNPs, higher levels of population differentiation, and a higher nonsynonymous-to-synonymous substitution ratio than the rest of the X chromosome. We show that the extent to which diversity is reduced is incompatible with direct selection or the action of background selection and soft selective sweeps alone, and therefore, we suggest that very strong selective sweeps have independently targeted these specific regions in several species. The only genomic feature that we can identify as strongly associated with loss of diversity is the location of testis-expressed ampliconic genes, which also have reduced diversity around them. We hypothesize that these genes may be responsible for selective sweeps in the form of meiotic drive caused by an intragenomic conflict in male meiosis.

X-chromosome evolution | great apes | selective sweeps | ampliconic genes | meiotic drive

Because beneficial and recessive X-linked mutations are fully exposed to selection in males, the X chromosome may experience increased rates of adaptive evolution (1, 2). For the same reason, a male-beneficial allele may be fixed by selection even when a deleterious effect in females far exceeds the advantageous effect in males (3), making the X chromosome a potential target of sexually antagonistic genes. These unique characteristics as well as the close evolutionary links between the X and Y chromosomes (4, 5) are likely to be responsible for the different gene content of the X chromosome compared with autosomes (6) and the higher nonsynonymous-to-synonymous substitution ratio in X-linked protein coding sequences compared with that of the autosomal ones (7, 8).

Several studies have indicated that the great ape X chromosome experiences more prevalent positive selection and more efficient purifying selection than the autosomes. Using McDonald–Kreitman-type analyses, we have previously reported that, in the Central chimpanzee lineage, 30–40% of amino acid changes on the X chromosomes are estimated to have been fixed by positive selection, whereas the autosomes do not show significant signs of positive selection (9). A similar conclusion was recently reached for the human X chromosome (10). In all great ape species, the X chromosome shows a more prominent decrease in nucleotide diversity around genes than the autosomes (11–14), interpreted as evidence for more efficient selection removing deleterious variants or fixing advantageous variants on the X

chromosomes. Recently, Arbiza et al. (14) showed that 14 human populations have similar relationships between the distance from genes and the diversity, suggesting comparable selective efficiency on the X and autosomes across human populations.

Here, we analyze X-chromosome data from the Great Ape Genome Diversity Project (11). Comparisons of X-chromosomes diversity patterns between the different species allow us to search for general properties of X-chromosome evolution. Surprisingly, we find that the diversity of the X chromosome is strongly reduced in megabase-wide regions in great ape species. We examine various possible explanations for this reduction in diversity and conclude that they are compatible only with recurrent hard selective sweeps affecting overlapping regions. We hypothesize that the targets are multicopy testis-expressed genes, which are overrepresented in the affected regions.

Results

We analyzed the polymorphism and divergence data of whole-genome sequences from 3 to 27 individuals from humans, bonobos, four chimpanzee subspecies, two gorilla species, and two orangutan species (Table S1). Filtering (*Methods*) leaves 1.93 Gb of the autosomes (67.4%) and 105.03 Mb of the X chromosome (67.8%), with 83,232,220 autosomal SNPs and

Significance

The X chromosome has a different inheritance pattern from the autosomes, direct interaction and potential conflict with the Y chromosome, and fewer copies than the autosomes. Natural selection may, therefore, act differently on the X chromosome. We analyze polymorphism patterns in 10 great ape species using 87 high-coverage whole genomes. We find that the X chromosome contains megabase-sized regions that are almost without variation in most species. No such regions are found on the autosomes. We suggest that independent and very strong selective sweeps are the only plausible explanation for these observations, and we hypothesize that the targets of these sweeps are multicopy testis-expressed genes in a genetic conflict with the Y chromosome for transmission to the next generation.

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2,289,265 X-linked SNPs (Table S2). The SNP quality scores on the X chromosomes are comparable with those on the autosomes (Fig. S1).

To contrast diversity patterns between autosomes and X chromosomes, we divided the dataset into exonic, intronic, and intergenic regions. We then estimated nucleotide diversity, π , for each functional category in each (sub)species (Fig. 1A). For both autosomes and X chromosomes, π is the lowest for exons followed by introns and then, intergenic regions. Contrasting X-chromosome and autosome diversity shows that the reduction on X, relative to that on autosomes, is largest for exons in all species.

We next correlated the intergenic diversity in nonoverlapping bins of 5 kb with physical distance to the nearest gene (Fig. 1B, Top). Similar studies in humans have used genetic mapping distance (11), but because a high-quality recombination map is only available for humans and the autosomes of Western chimpanzees and because recombination rates are known to change rapidly at the fine scale (15), we used physical distance. In all species, π increases with distance from the nearest gene, and this pattern extends farther than 100 kb away from genes in some of the species. The lower diversity around genes is more pronounced for the X chromosomes than the autosomes, which was illustrated by a positive correlation between distance to genes and the ratio of X to autosome diversity (Fig. 1B, Bottom). The latter observation is in line with previous studies reporting a stronger signature of selection on X chromosomes than on autosomes in humans and other great apes (11–14).

For each pair of species, we compared the slope of the diversity with the physical distance to the nearest gene using correlations of the physical distance from genes with the diversity ratio among pairs of species following the approach by Gottipati et al. (13). Demographic differences should not influence the relative slope, but a larger effect of selection on genes will lead to a steeper slope because of hitchhiking and background selection. For the autosomes, gorillas show the steepest relationships followed by orangutans, chimpanzees, bonobos, and humans (Fig. S2). Among the chimpanzees, Nigeria–Cameroon chimpanzees have the steepest slopes. For the X chromosomes, the ranking shifts, because humans have a steeper slope than bonobos, and Western chimpanzees now have the steepest slope among the chimpanzees. These results suggest that selection affects autosomes and X chromosomes differently among species. Among human populations, selection has been reported to affect the X and the autosomes in a similar way (14).

Diversity Patterns Along the X Chromosome. We next calculated π along the X chromosomes using nonoverlapping windows of 100 kb in size. The Eastern lowland gorilla shows an almost complete lack of polymorphism, and because only three X chromosomes were sampled, we chose to omit this species from subsequent analyses. Fig. 2 shows that π is highly variable along the X chromosomes in most species in contrast to similar analysis for autosomes (Fig. S3). We define low-diversity 100-kb windows as windows showing less than 20% of the average X-chromosome diversity, which are represented as black bars in Fig. 2 (the full distribution of π is shown in Fig. S4). We often observe several consecutive windows of low diversity (up to 1.8 Mb); such regions are not found on autosomes (Fig. S3). These regions often overlap among species and even genera, but most regions have normal levels of diversity in at least one species. Fig. 2 also shows the proportion of singletons among SNPs in 100-kb windows below the x axis. In many cases, there is a visible increase in the proportion of singletons in regions of low diversity (see Fig. 4).

Along the diagonals in Fig. 3, we show the proportion of low-diversity windows for autosomes and X chromosomes. The fraction of low-diversity windows is highest in the Bornean orangutan (13.2%) and lowest in the bonobo (0.07%) and the Nigeria–Cameroon chimpanzee (0.07%). Within the chimpanzees, the Western chimpanzee has the highest fraction of low-diversity windows (4.30%). The low-diversity windows are more abundant on the X chromosomes than on the autosomes by 1.95-

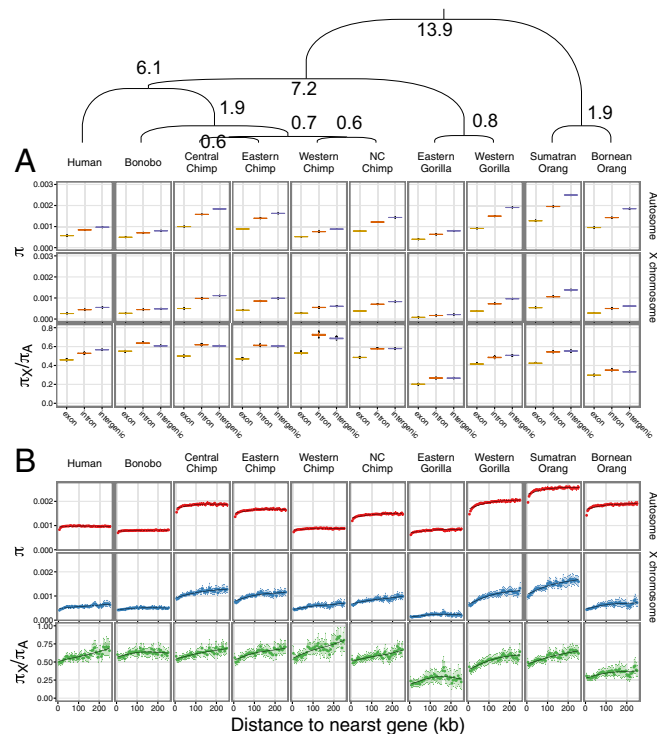


Fig. 1. Diversity levels inside and outside of genes on autosomes and X chromosomes. The phylogenetic relationship among all investigated great apes and the divergence times (in million years ago) are shown along the top. The nucleotide diversity of autosomes and X chromosomes and their ratio in (A) exons, introns, and intergenic regions and (B) 5-kb windows according to the distance from the nearest gene (95% confidence intervals from 1,000 bootstrapping iterations) are shown. NC, Nigeria–Cameroon.

to 36.30-fold, except for in the Nigeria–Cameroon chimpanzees (0.59-fold). Off-diagonal cells in Fig. 3 show the proportion of low-diversity windows in both members of a pair of species. The proportion of these is much larger for the X than the autosomes (overall 13-fold, $P < 10^{-16}$; one-tailed Fisher's exact test), and when we compare species from different genera, sharing is even larger (23-fold, $P < 10^{-16}$).

Evidence for Hard Selective Sweeps. To test whether the low-diversity windows can be partly explained by large genomic regions with lower mutation rates, we compared the divergence from the human reference genome in the low-diversity windows and the rest of the X chromosome. In most species, low-diversity windows also have a lower divergence compared with the rest of the X chromosome (Fig. S5A). However, this lower divergence does not necessarily imply a lower mutation rate. If the low diversity that we observe in the extant species is caused by selection, a similar effect could have reduced diversity in the ancestral species, which would then result in a lower divergence between the descendent species because of shorter coalescent time in the ancestor. The observed difference in divergence between low-diversity windows and the rest of X chromosomes is largest in chimpanzees (20.0%), intermediate in gorillas (9.7%), and lowest in orangutans (4.7%). This inverse relationship of divergence with phylogenetic distance from the human is expected if selection in the ancestral species explains the differences in divergence, because the proportion of time that lineages spend in the ancestral species is larger when the divergence is small. Therefore, selection is expected to contribute most to chimpanzees divergence and least to orangutan divergence, because the chimpanzees diverged most recently, and the orangutans diverged most anciently (11). To address this further, we estimated the diversity in the human–chimpanzee ancestor from the amount of incomplete lineage sorting (16)

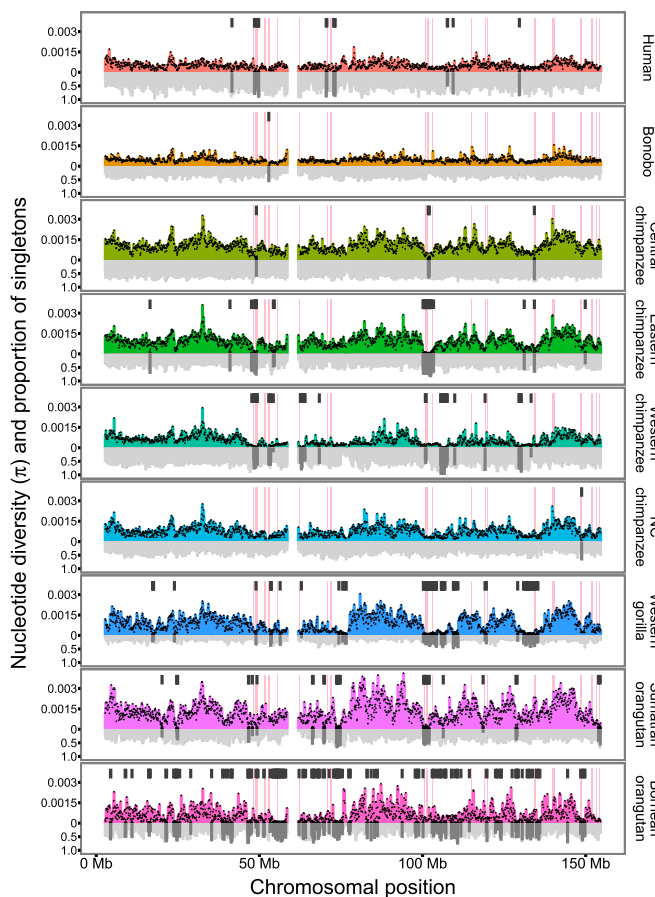


Fig. 2. Diversity and proportion of singletons along X chromosomes. The nucleotide diversity (colored bars with black dots) and the proportion of singleton polymorphisms among SNPs (gray bar) in nonoverlapping 100-kb windows of called sequence are shown for each species. Eastern lowland gorilla is omitted because of insufficient data. At the top of each panel, black bars indicate windows where the nucleotide diversity is less than 20% of the mean diversity for the X chromosome of the same species. The locations of ampliconic regions of human are shown as pink rectangles. NC, Nigeria–Cameroon.

(Methods). When this ancestral diversity is taken into account, the divergence for low-diversity regions is not significantly different from the rest of the X chromosome (Fig. S5B), arguing that the reductions in divergence are caused by selection in ancestral species rather than reductions in mutation rates.

Close inbreeding may also reduce the diversity locally in the genome (17). However, because we have a relatively large sample size and because the autosomes do not show similar patterns (Fig. S3), inbreeding is unlikely to contribute.

These results leave natural selection on the X chromosome as the sole explanation. Because at most, 10% of the genome seems to be under direct evolutionary constraint (18), reduction in diversity to less than 20% of the mean in large regions must mainly result from indirect selection in the form of background selection (negative selection) or hitchhiking (positive selection). We performed calculations based on existing theory (19) to estimate the expected maximal impact of background selection on diversity (details in SI Text). Within realistic ranges of selection coefficients and proportions of sequence under constraint, background selection is not expected to reduce diversity to less than 75% of the diversity (Fig. S6). To explain the observed levels of diversity, we need to assume a highly unrealistic fraction of the genome under direct selection (such as >80%). Furthermore, if background selection was solely responsible for reduced

diversity, we would expect the regions to be almost entirely shared among species.

Computer simulations of soft and hard sweeps, summarized in Table 1 (details in SI Text), show that, even with large selection coefficients (up to $s = 0.5$) and a low allele frequency at the onset of positive selection ($p_0 = 0.01$), soft sweeps would not reduce diversity to 25% of the chromosomal mean in regions larger than 200 kb (Fig. S7). Thus, a very large number of soft selective sweeps is required to explain the low diversity, and several independent soft sweeps would be needed to reduce diversity to 20% in a region larger than 1 Mb. With hard selective sweeps and effective population sizes in the range of 10,000–100,000, a selection coefficient of 0.1 is expected to reduce diversity to 75% of the original diversity in 1.7- to 2.2-Mb regions and 25% in regions of 400 kb only. For a single sweep to explain depressions below 25% in regions larger than 1 Mb, a selection coefficient larger than 0.5 is required. It is, therefore, more likely that the low-diversity regions on the X chromosome are the result of several sweeps.

Hard selective sweeps should cause distortions to the site-frequency spectrum. In particular, the fraction of singleton SNPs should be higher in the low-diversity regions than the regions with normal diversity in the presence of hard sweeps (20). In each 100-kb window, we computed the proportion of singletons and found that the low-diversity windows have a significantly higher proportion of singleton polymorphism (Fig. 4A). Tajima's D , which uses information from the complete site frequency spectrum, was found to be significantly lower in low-diversity regions than in the rest of the X chromosome, which is in agreement with the pattern of proportion of singletons (Fig. S5C).

We further estimated population divergence as the average allele frequency differences, which should be higher in regions affected by population-specific hard sweeps (21), between six pairs of four chimpanzee subspecies and two orangutan species (Methods). Absolute population divergence is significantly higher in low-diversity regions than in the rest of the X chromosome in all comparisons (Fig. 4B). A similar pattern is seen for population divergence measured by F_{ST} (Fig. S5D).

Finally, we contrasted the ratio of nonsynonymous to synonymous substitutions between low-diversity windows shared by multiple species and the remaining X chromosome. Nucleotide substitutions were identified by comparing a nucleotide of each species with an ancestral allele of the great apes, and whether a substitution was nonsynonymous or synonymous was determined by the comparison with the human annotation. Then, we counted the number of nonsynonymous and synonymous substitutions observed in the phylogenetic tree of the great apes. The windows with low diversity have a higher nonsynonymous-to-synonymous

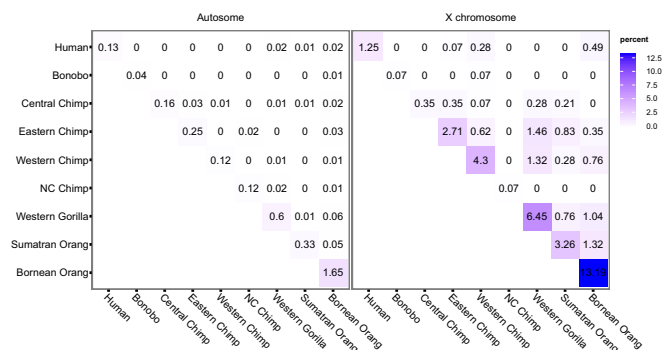


Fig. 3. Proportion of shared regions with reduced diversity. Heat maps for the proportion of shared 100-kb windows with reduced diversity among species in the autosomes and the X chromosomes. The diagonal shows the percentage of windows with less than 20% of the chromosomal average π . The off-diagonal cells show the percentage of windows satisfying this condition in both of two species. NC, Nigeria–Cameroon.

substitution ratio than the rest of X chromosome by 23.3% ($P = 0.0002$; one-tailed Fisher's exact test). The overrepresented nonsynonymous substitutions in the low-diversity windows are compatible with both increased positive selection on protein changes and relaxed purifying selection caused by indirect selection and different gene content of these regions.

Effect of Recombination Rate. The physical extent of a selective sweep is inversely correlated with recombination rate, and the power to observe them is, therefore, higher in regions of low recombination (22). We, therefore, contrasted the recombination rate from the human recombination map from pedigree data (23) in low-diversity regions with the rest of the X chromosome. The recombination rate of low-diversity regions is between 22.6% and 74.1% of the recombination rate in the remainder of the X chromosome in the different species, except Nigeria–Cameroon chimpanzees, in which the recombination rate is higher by 58.4% in the low-diversity regions (Fig. S5E). Regions in which at least one species has low diversity have an average recombination rate of 65.8% for the rest of the X chromosome. We conclude that reduced recombination of low-diversity regions contributes to their physical extent approximately by a factor of two.

Low-Diversity Regions Associated with X-Linked Ampliconic Regions. If the low-diversity regions are the result of hard selective sweeps, it is puzzling why sweeps of such magnitude would be private to the X chromosome. We searched for associations between the low-diversity windows and X chromosome-specific properties. We first performed a gene ontology analysis to test whether genes in specific functional categories are overrepresented in the overlaps of low-diversity windows but found no gene ontology term to be significantly overrepresented.

We next considered X-linked ampliconic genes. Mueller et al. (24) recently characterized this X-specific phenomenon in detail. In humans, the X chromosome has 27 independent regions of 100–700 kb in size that contain multiple >99% identical copies of protein coding genes, which are predominantly or exclusively expressed in testis. Only 31% of ampliconic genes are shared

Table 1. Diversity reduction by soft and hard sweeps

	Hard sweep		Soft sweep			
	To 75%	To 25%	$p_0 = 0.01$		$p_0 = 0.1$	
			To 75%	To 25%	To 75%	To 25%
10,000						
0.01	0.3	0.1	0.4	<0.1	0.1	<0.1
0.05	1.4	0.2	1.0	0.2	0.3	<0.1
0.1	2.2	0.4	1.4	0.2	0.3	<0.1
0.2	4.1	0.8	1.9	0.3	0.3	<0.1
0.5	10.2	2.4	2.5	0.2	0.2	<0.1
50,000						
0.01	0.3	0.1	0.2	<0.1	0.1	<0.1
0.05	1.0	0.2	0.4	0.1	0.1	<0.1
0.1	1.7	0.4	0.5	0.1	<0.1	<0.1
0.2	3.5	0.6	0.5	0.1	0.1	<0.1
0.5	9.0	1.8	0.5	0.1	0.1	<0.1
100,000						
0.01	0.2	<0.1	0.1	<0.1	<0.1	<0.1
0.05	0.9	0.2	0.2	<0.1	<0.1	<0.1
0.1	1.7	0.4	0.2	<0.1	<0.1	<0.1
0.2	3.0	0.7	0.3	<0.1	<0.1	<0.1
0.5	8.3	1.7	0.3	<0.1	<0.1	<0.1

Summary of expected length of reduced diversity (in megabases) caused by soft and hard sweeps as a function of effective population size (N), selection coefficient (s), and the proportion of beneficial allele onset of selection (p_0). Details are in [SI Text](#).

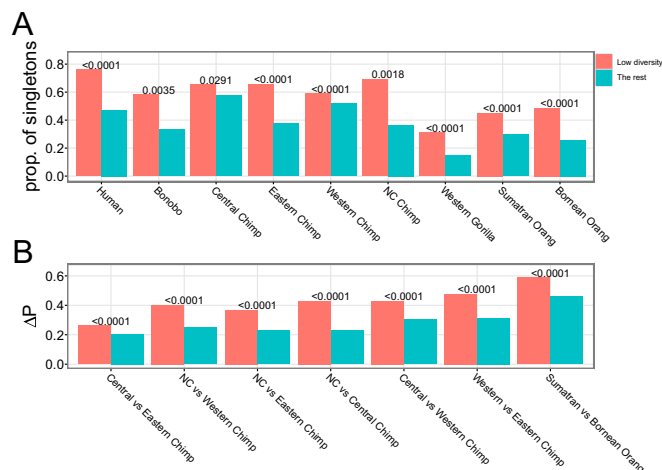


Fig. 4. Evidence for hard sweeps. (A) The proportion of singleton polymorphisms in SNPs and (B) population differentiation (ΔP) between six pairs of four chimpanzee subspecies and two orangutan species. The differences in the two statistics between regions of reduced diversity (red) and the remaining X chromosome (green) were tested using one-sided bootstrapping tests with 10,000 replicates, and P values are shown above each pair of bar plots. NC, Nigeria–Cameroon.

with mouse compared with 95% for single-copy genes (24), showing a rapid turnover of these regions. In the mouse, these genes are expressed postmeiotically (25). The ampliconic regions show a striking concordance with low-diversity regions that are most strongly affected by selection in the species (Fig. 2, pink rectangles). To test whether ampliconic genes are associated with lower diversity in regions around them, we contrasted π in the flanking regions of the amplicons (100 kb and 1 Mb) with the rest of the X chromosome. In all species, we observe that π is significantly lower in the flanking regions than in the rest of the X chromosome (Fig. 5). The diversity is difficult to estimate reliably in the ampliconic regions (Fig. S8A), because estimates may be biased by mapping artifacts caused by the repetitive nature of the ampliconic regions; therefore, we put more emphasis on the signatures in the flanking regions presented in Fig. 5. We do not detect a difference in the proportion of singleton polymorphisms between the flanking regions of the amplicons and the rest of the X chromosome (Fig. S8B) but find a higher level of population differentiation in all available (sub)species comparisons (Fig. S8C). Finally, we tested using Fisher's exact tests whether the flanking regions contain a higher proportion of low-diversity 100-kb windows than the rest of the X chromosomes. We found that low-diversity windows are overrepresented in the flanking regions in all species (Fig. S8D).

Discussion

We have presented the observation that large regions of the X chromosome and not the autosomes have strongly reduced diversity in the great apes. Because unique characteristics of the X chromosome (such as GC content or repeat density) might cause lower sequence quality, we did several tests to investigate whether biases in mapping and SNP calling could potentially contribute to this result. We find that low-diversity windows have a higher SNP quality score than the rest of the regions of the X chromosome (8,276 for low diversity and 7,801 for the rest, $P < 0.0001$; one-tailed bootstrapping test). The proportion of variants removed by filtering is slightly lower in low-diversity windows but not significantly so (22.2% for low diversity and 23.0% for the rest of the X chromosome, $P = 0.0643$). We also found that the low-diversity windows have a comparable proportion of included sequence to the rest of windows (73.0% for low diversity and 72.6% for the rest, $P = 0.6689$). Thus, sequencing and

calculated as follows: (i) for each position, we calculated the distance from the nearest transcript, (ii) the positions were sorted by the distance, (iii) the positions were grouped according to the distance by 5 kb, and (iv) π was calculated for each group. The 95% confidence intervals were obtained by the nonparametric bootstrapping resampled among 1-Mb nonoverlapping windows with 1,000 replicates.

Divergence Normalization in *Pan*. The average of density of sites with X-chromosomal incomplete lineage sorting between human and chimpanzee is 10.26% (16), which corresponds to the ancestral effective population size ($N_{e,Ans}$) of humans, bonobos, and chimpanzees that is equal to 54,103. The $N_{e,Ans}$ of reduced diversity windows was estimated with the ratio of the diversity in these windows to diversity of the rest of windows. The $N_{e,Ans}$ of the rest of windows on the X chromosomes was estimated in the same way. The number of generations between extant humans and each *Pan* species ($N_{gen,H-BC}$) was calculated by

$$N_{gen,H-BC} = n_{gen,BC} \times 2 + N_{e,Ans} \times 2,$$

where $n_{gen,BC}$ is the number of generations in bonobo–chimpanzee lineage after complete split from human lineage. We inferred $n_{gen,BC}$ to be 244,000 based on assumptions that the speciation time is 6.1 Mya and the generation time is 25 y. The divergence levels were normalized by dividing the D_{XY} values (45) with the relative differences of $N_{gen,H-BC}$ between low-diversity windows and the rest of windows.

The Putative Sweep Analysis. We calculated π in nonoverlapping 100-kb windows across the genome and excluded windows where less than 20% of the sites were called.

The index of allelic differentiation (ΔP) between populations A and B was calculated using the following formula:

$$\Delta P = \frac{\sum_i |AF_{A,i} - AF_{B,i}|}{no. SNP},$$

where $AF_{A,i}$ and $AF_{B,i}$ are the allele frequencies of the i th SNP in populations A and B, respectively, and $no. SNP$ is the total number of SNPs in the window. The F_{ST} values are calculated using the methods by Weir and Cockerham (46) with the Genepop software (47).

The calculations on the possible effects of background selection and the simulations to explore selective sweeps are described in [SI Text](#). The list of ampliconic regions was obtained from the literature (24). The gene ontology test was performed using the GOrilla software (48).

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