

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

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Edited by Daven C. Presgraves, University of Rochester, Rochester, NY, and accepted by the Editorial Board March 16, 2015 (received for review November 11, 2014)

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.

Author contributions: K.N. and M.H.S. designed research; K.N., K.M., A.H., J.Y.D., T.M., and M.H.S. performed research; K.N., K.M., A.H., J.Y.D., K.R.V., A.E.W., M.F.H., G.A.G.D.P., T.M., and M.H.S. analyzed data; and K.N. and M.H.S. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission. D.C.P. is a guest editor invited by the Editorial Board.

Freely available online through the PNAS open access option.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1419306112/-DCSupplemental.

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-

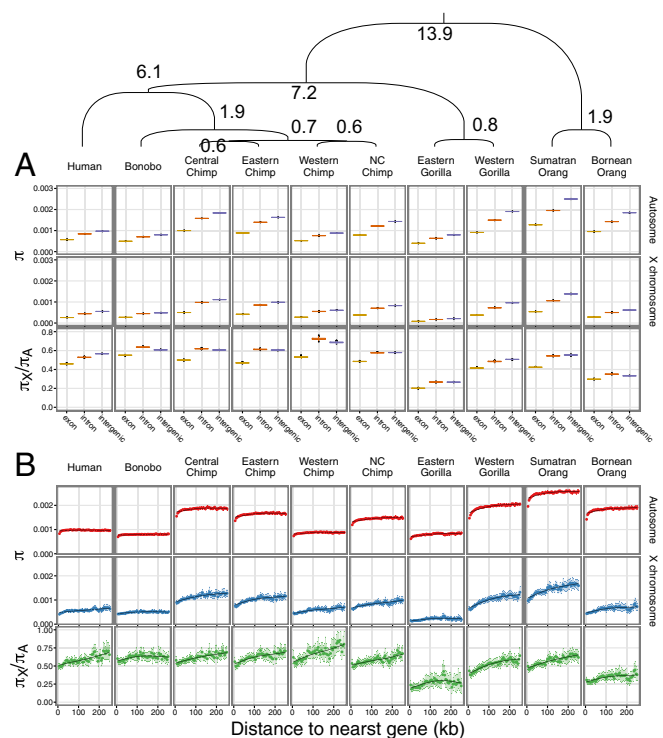


Fig. 1. Diversity levels inside and outside of genes on autosomes and X chromosomes. The phylogenetic relationship among all investigated great apes and the divergence times (in million years ago) are shown along the top. The nucleotide diversity of autosomes and X chromosomes and their ratio in (A) 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)

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

| Ne and s | Hard sweep | | Soft sweep | | | |
|----------|------------|--------|-----------------|--------|----------------|--------|
| | To 75% | To 25% | $\rho_0 = 0.01$ | | $\rho_0 = 0.1$ | |
| | | | 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 (ρ_0). Details are in SI Text.

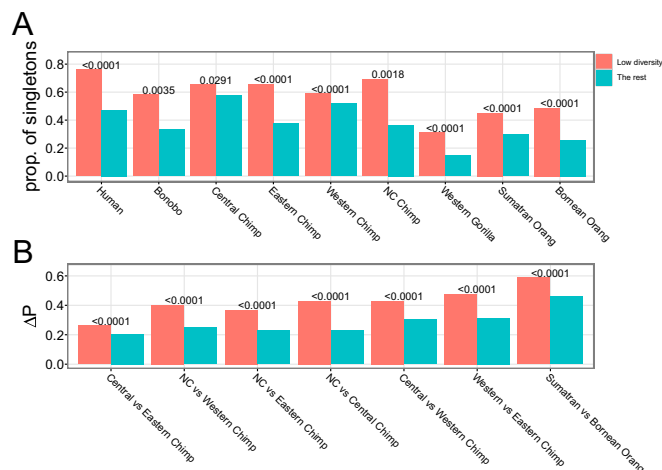


Fig. 4. Evidence for hard sweeps. (A) The proportion of singleton polymorphisms in SNPs and (B) population differentiation (ΔP) between six pairs of four chimpanzee subspecies and two orangutan species. The differences in the two statistics between regions of reduced diversity (red) and the remaining 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

mapping artifacts do not seem to differ in a way that can explain our observations.

Our analysis suggests that the X chromosomes of the great apes are targets of exceptionally strong positive selection recurrently affecting orthologous targets over many megabases. The strongest selective sweep observed in human populations is associated with the lactase gene and has an estimated selection coefficient of 9–19% in the Scandinavian population (26). Even this level of selection affects diversity only in an 800-kb region.

In a search for X chromosome-specific phenomena that could cause recurrent sweeps, we found that, in all species, low-diversity regions strongly associate with the positions of X-linked ampliconic regions, assuming that all species have ampliconic regions in the same places as in the human genome. The function of genes in ampliconic regions is not well-understood, but their evolution seems to be very dynamic, and it is likely that copy number changes often occur, because only 31% of ampliconic genes are shared between human and mouse compared with 95% for single-copy genes (24). The ampliconic genes are expressed predominantly in testis, and therefore, it is tempting to hypothesize that X-linked ampliconic regions are associated with selection for gene expression at some stage during or after male meiosis. We hypothesize that such selection could mediate an intragenomic conflict with Y-linked elements. In this scenario, duplication in an X-linked ampliconic region would be strongly selected if this results in the preferential transmission of the X chromosome. We believe that recurrent segregation distortions of several percentages are more easily envisioned than similar selection coefficients acting on organismal fitness alone. In response to the fixation of a segregation distorter, any compensatory mutation on the Y chromosomes will be under very strong selection to balance the sex ratio as shown from theoretical prediction (27–29) and in empirical observations from *Drosophila* (30–32).

In line with this conjecture, correlated gene amplification in mouse between sexually antagonistic X-linked *Slx* genes and Y-linked *Sly* genes in rodents has been suggested to be a consequence of intragenomic conflict between X and Y chromosomes to balance the sex ratio (33–35). A recent report in mouse also suggests that amplification of Y-linked ampliconic genes is driven by the gene amplification of the gametologous X-linked gene pairs to restore an optimal sex ratio (36). However, in great apes, ampliconic regions on the Y and X are of different origin (37, 38), suggesting that a mechanism to adjust sex ratio may not involve correlated amplification between gametologous gene pairs.

The great ape species differ greatly in their demographic history, long-term effective population sizes, and breeding systems. Each of these factors potentially plays a role in the extent

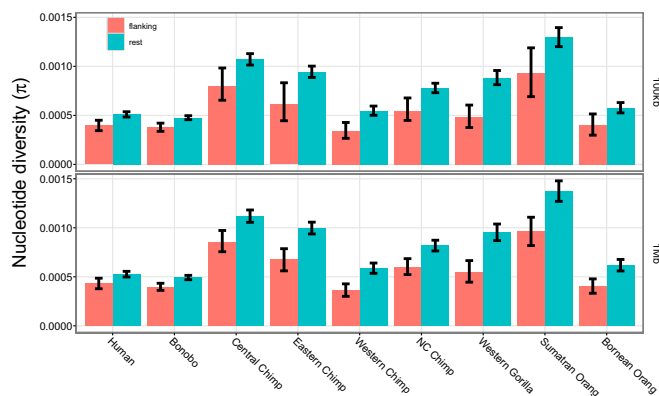


Fig. 5. Diversity around ampliconic regions. *Upper* shows π in the 100-kb flanking regions of the amplicons and the rest of the X chromosome in each species. *Lower* shows the same but for 1-Mb flanking regions. The error bars indicate 95% confidence intervals from 1,000 bootstrapping iterations resampled from 1-Mb windows. NC, Nigeria–Cameroon.

of selective sweeps depending on the underlying mechanism. The widest regions of diversity loss on the X chromosomes are found in Western lowland gorillas and orangutans followed by chimpanzees and humans and finally, bonobos. Among the chimpanzees, the Western chimpanzee has the widest regions, with reduced diversity on the X chromosomes. Thus, the width and combined size of the regions with reduced diversity do not generally reflect population size estimates, where gorillas and orangutans have similar effective population sizes as Central chimpanzees and the Western chimpanzee has a smaller effective population size than the other chimpanzees (11). The expected width of a specific selective sweep is smaller in a large population than in a small population, because the time to fixation is shorter in a small population (Table 1). However, if the occurrence of new mutations limits the number of selective sweeps, the total effect of sweeps is dependent on census population size rather than effective population size. In addition, for sufficiently strong selective sweeps, the probability of fixation is almost completely determined by the selection coefficient and only weakly dependent on effective population size.

The correlation between regions of reduced diversity and testis-expressed ampliconic regions suggests two possible mechanisms creating repeated signatures of selective sweeps: meiotic drive and sperm competition. Under sperm competition, we expect most sweeps in species with more sperm competition, whereas under meiotic drive, the prediction is reversed, because sex chromosome meiotic drive has been reported to lead to reduction in production of either X or Y carrying sperms (39, 40); strong sperm competition may, thus, reduce the effect of meiotic drive, because sperm containing a driving variant will be disadvantageous in the competition among males. Among the great ape species, using the ratio of testicle to body weight as a proxy for sperm competition, gorillas have the least sperm competition followed by orangutans, humans, chimpanzees, and then, bonobos (41, 42). This ordering of species is negatively correlated with the proportion of reduced diversity windows (Spearman's $\rho = -0.72$, $P = 0.028$) (Fig. S9), which fits the prediction of meiotic drive.

We also note that orangutans have many reduced diversity regions that do not coincide with the positions of human ampliconic regions. However, the orangutan is phylogenetically most distant from humans, from whom the positions of ampliconic regions are taken. Dynamic evolution of these regions would predict an inverse relationship between phylogenetic distance and extent of overlap to human ampliconic regions. Our hypothesis that ampliconic regions are responsible for extreme loss of diversity can be tested by determining the species-specific positioning of ampliconic regions rather than using the positions in the human genome. We predict that the association should increase if the hypothesis is true. Direct expression analyses at different stages during spermatogenesis and individual differences may also reveal whether escape from meiotic sex chromosome inactivation (25) or interference with XY body formation is a source of meiotic drive.

Methods

Preparation of the Dataset. We used the pipelines and the variants from the Great Ape Genome Diversity Consortium (biologiaevolutiva.org/greatape/data.html) (11). The sequences were mapped against hg18. We excluded all positions that were not called in all of the great ape species. Then, we excluded pseudoautosomal regions of X chromosomes. All heterozygous positions on X chromosomes in at least one male were also excluded.

The sequences were annotated with refSeqGenes downloaded from the table browser at the UCSC Genome Bioinformatics Site (genome.ucsc.edu/index.html). If any position can be included as multiple functional categories, we annotated the position with the following priority: exons, introns, and intergenic sequences. The nonsynonymous and synonymous variants were determined using ANNOVAR software (43).

Diversity Estimation. The nucleotide diversity, π , was calculated using the formula by Nei and Li (44) on the variants called in the Great Ape Genome Diversity Consortium that passed the variant filtering used there (11). For exons, introns, and intergenic sequences, we calculated π separately. The diversity according to the physical distance from the nearest gene was

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

$$N_{gen_{H-BC}} = ngen_{BC} \times 2 + N_{e_{AnS}} \times 2,$$

where $ngen_{BC}$ is the number of generations in bonobo–chimpanzee lineage after complete split from human lineage. We inferred $ngen_{BC}$ 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.

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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).

ACKNOWLEDGMENTS. We thank Brian Charlesworth, Andy Clark, David Reich, and Freddy B. Christiansen for comments on the manuscript. The work was supported by the European Commission-funded 7th Framework Programme for Research and Technological Development NEXTGENE Project (to T.M. and M.H.S.) and a grant from the Danish Council for Independent Research (to M.H.S.).

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