Natural selection reduced diversity on human Y chromosomes

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Y diversity

The human Y chromosome exhibits surprisingly low levels of genetic diversity. This could result from neutral processes if the effective population size of males is reduced relative to females due to a higher variance in the number of offspring from males than from females [1]. Alternatively, selection acting on new mutations, and affecting linked neutral sites, could reduce variability on the Y chromosome [2]. Here, using genome-wide analyses of X, Y, autosomal and mitochondrial DNA, in combination with extensive population genetic simulations, we show that low observed Y chromosome variability is not consistent with a purely neutral model. Instead, we show that models of purifying selection are consistent with observed Y diversity. Further, the number of sites estimated to be under purifying selection greatly exceeds the number of Y-linked coding sites, suggesting the importance of the highly repetitive ampliconic regions. Because the functional significance of the ampliconic regions is poorly understood, our findings should motivate future research in this area.

Human resequencing data

Complete Genomics human resequencing
- 16 unrelated males
- 8 Africans, 8 Europeans

Autosomes, X, Y and mtDNA from the same individual eliminates one source of sampling variation. Diversity is corrected for different mutation rates on A, X, Y and mtDNA using human-chimpanzee divergence estimates.

Chr	African observed	African modeled	European observed	European modeled
autosomes	0.0739	0.0733	0.0563	0.0563
chrX	0.0601	0.0565	0.0365	0.0402
chrY	0.0018	0.0223	0.0024	0.0101
mtDNA	0.0278	0.0222	0.0170	0.0101

Table 1. Observed and modeled estimates of diversity (pi) normalized by human-chimpanzee divergence to correct for variations in mutation rates across genomic regions.

Testing neutral demography

Expected ratios of diversity (X/autosome, Y/autosome and mtDNA/autosome) were computed from mean diversity estimates from 10000 ms simulations using different demographic histories for Africans and Europeans, first assuming equal numbers of males and females (N_m/N_f = 1), then successively skewing the effective number of males relative to females in each population (e.g. N_m/N_f = 0.75 implies three males for every four females in the population).

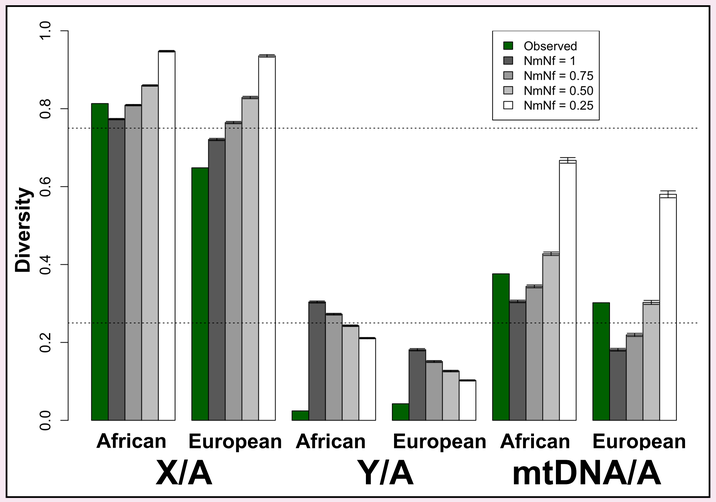


Figure 1. Observed and expected ratios of normalized X/Autosome, Y/Autosome, and mtDNA/Autosome nucleotide diversities.

Purifying selection

Neutral demography alone (variation in male reproductive success) is not sufficient to explain low Y diversity. Purifying selection acting on linked neutral sites (background selection) can reduce diversity across the entire Y. Approximate likelihood approach
- Forward simulations (SFS_CODE)
- Demography, Purifying selection

Investigate two sets of models:
1. Selection on coding sites only
2. Selection on coding and noncoding regions

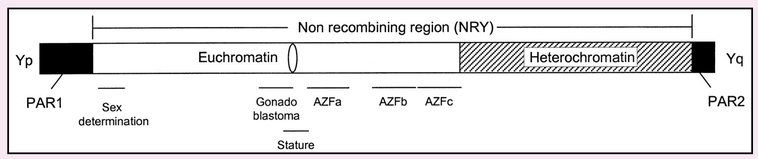
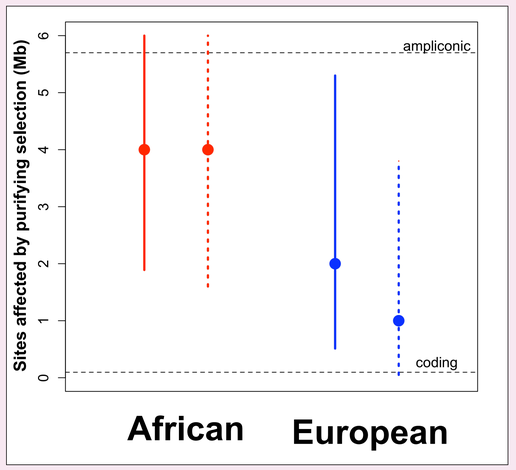


Figure 2. There is no recombination across most of the Y chromosome, so nearly all sites are linked. Image from Foresta *et al.* (2001)

Sites affected by selection

Given its unique structure, it is possible that purifying selection acts on more than just the nonsynonymous sites on the Y chromosome. Specifically, in addition to the approximately 100,000 single copy coding sites, the Y also contains 5.7Mb of highly repetitive ampliconic regions, each with nearly-identical expressed exclusively in the testis [3], and so may be under selection related to male fertility. Further, in the absence of homologous recombination with the X, intra-chromosome pairing and the resulting gene conversion between palindrome arms may reduce the mutational load on the Y, and so these palindromes themselves, as a means of allowing intra-chromosome recombination, may be subjects of selection [3,4].



MLE (95% CI)

N_m/N_f = 1 (solid)
African:
5 (1.36-6) Mb
European:
3 (0.798-6) Mb

N_m/N_f = 0.38 (dotted)
African:
5 (1.85-6) Mb
European:
2 (0.18-4.2) Mb

Figure 3. Maximum likelihood estimates of the number of sites affected by purifying selection on chrY.

Conclusions

- Chromosome-wide diversity on the human Y is extremely low.
- Lower male reproductive success cannot account for low Y diversity and genome-wide patterns of diversity.
- Low Y diversity is consistent with background selection.
- Ampliconic regions are likely affected by selection.

References

1. Hammer et al. 2008
2. Rozen et al, 2009
3. Skaletsky et al. 2003
4. Marias et al. 2010

Acknowledgments

Many thanks Miller Institute for Basic Research in Science for supporting this research.