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Should Y stay or should Y go: The evolution of non-recombining sex chromosomes

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Abstract

Gradual degradation seems inevitable for non-recombining sex chromosomes. This has been supported by the observation of degenerated non-recombining sex chromosomes in a variety of species. The human Y chromosome has also degenerated significantly during its evolution, and theories have been advanced that the Y chromosome could disappear within the next ~5 million years, if the degeneration rate it has experienced continues. However, recent studies suggest that this is unlikely. Conservative evolutionary forces such as strong purifying selection and intrachromosomal repair through gene conversion balance the degeneration tendency of the Y chromosome and maintain its integrity after an initial period of faster degeneration. We discuss the evidence both for and against the extinction of the Y chromosome. We also discuss potential insights gained on the evolution of sex-determining chromosomes by studying simpler sex-determining chromosomal regions of unicellular and multicellular microorganisms.

Keywords

evolution; sex chromosome; microorganism

Introduction

It has long been recognized that meiotic recombination between homologous sex chromosomes is repressed in species with heterogametic sexes (e.g. between X and Y in mammals and between Z and W in birds). For instance, it has been shown that in humans there is no recombination between the X and Y chromosomes during meiosis, except within the small defined pseudoautosomal regions (PAR) located at the tips of the X and Y chromosomes. Repression of recombination is thought to be advantageous during the early stages of sex chromosome evolution, when sex-determining factors first emerged on a pair of homologous autosomes. This serves to maintain gene/allele combinations critical for sex determination and sexual antagonism. However, the lack of meiotic recombination, together with reduced effective population sizes (N_e), pose serious threats to the long-term evolutionary viability of these non-recombining sex chromosomes. It has even been suggested that the degenerating partner might be lost eventually.

The non-recombining sex chromosomes degenerate

Sex chromosomes that are only present in the heterogametic sexes (e.g. the Y chromosome in male mammals and the W chromosome in female birds) are largely bereft of meiotic recombination (X or Z chromosomes can still undergo typical meiotic recombination with their counterparts in the homogametic sex), and experience a severe reduction in their N_e

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(the N_e of X or Z is three times those of Y or W, respectively). Because of this, the Y and W chromosomes are prone to random genetic drift, and natural selection against deleterious mutations is no longer as efficient as that acting upon autosomes (Figure 1). As a result, the long-term evolutionary trajectories of these non-recombining sex chromosomes have been predicted to be a gradual genomic decay with accumulation of deleterious mutations and gene losses. This prediction is consistent with the observation that Y (or W) chromosomes in many species have undergone significant degeneration. For instance, compared to the human X chromosome, which is ~150 Mb in size and contains ~800 genes, the human Y chromosome is only ~23 Mb in size and contains only ~80 genes [1,2]. Studies have shown that degeneration of these non-recombining sex chromosomes starts soon after they cease to recombine. For example, analyses of the neo-Y chromosomes in *Drosophila miranda* (formed ~1 million years ago), as well as in the black muntjac (formed ~0.5 million years ago) revealed these incipient sex chromosomes have already accumulated considerable levels of mutation and degeneration [3–5]. Additionally, it has been shown that this gene loss process is not random, suggesting that there is a certain level of selection counteracting the degeneration process [6].

Although the degeneration of the non-recombining sex chromosome seems inevitable, the rate of this degradation may vary in different species, and the degeneration process can be complex. For example, in *Silene latifolia*, the white campion in which sex chromosomes were formed about 10 million years ago, recent studies have shown that a large fraction of the genes on the Y chromosome are still functional. At most only ~20% of all of the ancestral genes have been lost from the Y chromosome [7,8]. This slower degeneration rate of Y chromosomes in plants compared with animals could be due to strong haploid purifying selection in plants, as well as the existence of dosage compensation in animals (although a recent study argues that dosage compensation also exists in *Silene latifolia* [9]). A recent study of European tree frogs, *Hyla arborea*, suggested that in this species the lack of decay of the Y chromosome, which is homomorphic with the X chromosome, is most likely maintained by occasional X-Y recombination (which may occur occasionally in sex-reversed females). Selective sweeps by the newly arisen recombinant Y chromosomes may also reduce the levels of deleterious mutations and prevent Y from degenerating [10].

Nevertheless, complete loss of the Y chromosomes is possible. In fact, recycling of Y chromosomes by emergence of neo-sex chromosomes (either through translocation of sex determining elements onto an autosome, or fusion of the Y chromosome remnant with an autosome) have been observed in a variety of species of insects, fishes, birds, mammals, as well as plants [5,11–17].

Is the human Y chromosome also doomed?

As to the human Y chromosome, studies have shown that since the emergence of mammalian sex chromosomes about 160 million years ago, the Y has lost most of the ancestral genes that were once located on it. Estimates based on the number of genes that the human Y chromosome has lost during its evolution provide a lifespan estimation for the human Y chromosome, predicting its demise as early as 4.6 million years from now [18].

Recently, several studies have challenged the hypothesis that the human Y chromosome is on its way toward inevitable extinction. Analyses of the Y chromosomes from human and related species examining their retention of ancestral gene contents show evidence of surprisingly conservative evolution of the human Y chromosome [19–21]. Specifically, a careful study of the gene content within different strata of the human Y chromosome shows that the human Y chromosome has not lost any genes since the human and chimpanzee lineages split (~6 million years ago). The Y has also retained most of the ancestral genes

present at the split of the human-chimpanzee and rhesus lineages (~25 million years ago). Additionally, no gene loss has occurred within the strata of the human Y chromosome that were formed before it split from the chimpanzee lineage. These findings suggest that the gene contents of these old strata have been very stable over a fairly long evolutionary timeframe [20]. This surprisingly conservative evolution prompted the authors to conclude that although the human Y chromosome experienced fast evolution including rapid gene loss at the early evolutionary stages, this process has slowed significantly, and may have even ceased, during its recent evolution after the split between the old world monkey and the last common ancestor of human and chimpanzee. If so, how did the human Y chromosome manage to keep its genes intact during this long period of evolution despite all of the forces that drive its otherwise inexorable degeneration? Several factors could have contributed to this stability.

First is strong purifying selection (Figure 1). As mentioned earlier, purifying selection at the haploid stage has been invoked to explain the slower degeneration observed in plant Y chromosomes [7,8]. Despite the significantly reduced effective population size of the Y chromosome, a recent study of the single copy genes in the male specific region of the human Y chromosome revealed remarkably low levels of amino acid variation among more than 100 men representing worldwide diversity, suggesting that strong purifying selection is acting upon these genes [22]. Additionally, the authors found a lower level of diversity in these genes compared to theoretical predictions. This suggests that the Y chromosomes have a further reduced effective population size, which may have resulted from the higher variance in reproductive success among men than among women [22].

Besides strong purifying selection, it has been shown that many genes on the human Y chromosome have multiple copies that form palindromes, which could increase the population sizes of these genes. Additionally, abundant gene conversion occurs between the arms of these palindromes, which slows the accumulation of deleterious mutations and counteracts degeneration of the Y chromosome by enabling intrachromosomal repair [23] (Figure 1). Gene conversion has also been recently found to be widely distributed within the centromere cores of maize [24], as well as within the highly rearranged mating type locus of *Cryptococcus neoformans*, a human pathogenic fungus ([25], see also below). Hence gene conversion might play an important role in the evolution of these chromosomal regions within which traditional meiotic recombination was thought to be repressed. Gene conversion can be directional. Biased gene conversion in favor of G or C (GC-biased gene conversion, gBGC) has been well characterized in mammals, birds, fruit flies, fishes, and grasses [26–29]. Additionally, gene conversion that is biased against new mutations has been proposed to explain the observed slower mutation rate in plants and bacteria [30,31]. An example is the 16S rDNA clusters in bacteria and the 18S rDNA cluster in fungi. rDNA is diverged between lineages, while highly conserved within lineages. Additionally, conservation is also maintained among the copies of the rDNA within each lineage. It is not yet fully clear how this conservation is maintained. A process called concerted evolution, which involves ectopic recombination and gene conversion between different copies of the rDNA within the cluster, underlies the observed homogenization among rDNA copies. Thus, gene conversion maintains the integrity of the duplicated units by preventing accumulation of substitutions, even in the absence of traditional meiotic recombination. Furthermore, recent simulation-based, as well as population genetics studies, suggest that even low levels of gene conversion are sufficient to maintain the sequence integrity of the genes located on the Y chromosome [32,33].

The evolution of the mating-type locus (*MAT*) in unicellular microorganisms

Most of the work on sex chromosome evolution has focused on multicellular organisms. However, most unicellular microorganisms also engage in sexual reproduction. Some microorganisms even possess fairly complex mating type determining chromosomal regions that mirror the sex chromosomes of multicellular eukaryotes. Additionally, evolutionary forces that shape mammalian sex chromosome evolution also act upon mating type loci of microorganisms. We next discuss what has been learned about the evolution of mating type determining chromosomal regions in unicellular microorganisms, such as fungi, algae, slime molds, and other protists. This perspective can help us to better understand the evolution of sex chromosomes in multicellular eukaryotes.

Many fungal species can undergo sexual reproduction when individuals with compatible mating types encounter each other. Fungal mating types are established by a chromosomal region called the mating-type locus (*MAT*) that contains several key mating-type identity genes. The presence of the *MAT* locus can affect the evolutionary trajectories of the genes located on the same chromosome in yeast species [34,35]. In a recent study, it was found that the key sex determinant in both the zygomycete fungi, as well as in some ascomycetous fungi, is an HMG domain protein in the same family as the mammalian *SRY* sex determinant of mice and men, revealing a striking homology in the sex determining system between unicellular microorganisms and multicellular animals [36]. In contrast, the *MAT* loci of some fungal species encode pheromones and pheromone receptors, whereas mammalian sex chromosomes are not known to do so, demonstrating that unique features are present in the sex determining chromosomal regions of these species.

Studies have also revealed that for some fungal species, the *MAT* locus can be unusually large. For example, in *Ustilago hordei*, a pathogen of small-grain cereals, the *MAT* locus spans ~500 kb, more than 15% of the ~2.8 Mb chromosome on which it resides [37,38]. Another example is the human pathogenic *Cryptococcus* species complex, which consists of four different serotypes (A, B, C, and D) belonging to at least two species (*C. neoformans* and *C. gattii*). The mating-types of these species are controlled by a large *MAT* locus that is ~100–120 kb in length (~6% of the length of the chromosome on which it resides) and contains more than 20 active genes [39,40]. Mating typically occurs between individuals possessing different alleles at the bi-allelic *MAT* locus, although unisexual mating between partners with identical mating type also occurs [41].

Recent studies have shown there are extensive chromosomal rearrangements between the opposite *MAT* alleles within each species. The *MAT* locus of different species within the pathogenic *Cryptococcus* species complex have undergone extensive rearrangements after these lineages split from each other some 40 – 80 million years ago [39,40,42–44]. Meiotic recombination has been thought to be repressed within the *MAT* locus due to the extensive chromosomal rearrangements and sequence divergence. However, gene conversion has recently been detected within a GC rich intergenic region located within *MAT* [45].

Additionally, the *MAT* locus of *C. neoformans* shows signs of convergent evolution with the sex chromosomes in animals. First, sex determinants emerge on autosomes and then are captured onto sex chromosomes or into *MAT*. Second, both sex chromosomes and the *MAT* locus underwent stepwise expansion during their evolution, resulting in strata of distinct evolutionary ages. Third, there is coherence of genes functioning involved in sex determination, sexual antagonism, and sexual reproduction. Fourth, sex/mating type unique genes are duplicated in inverted palindromic repeats, enabling repair by intrachromosomal recombination (e.g. gene conversion). Fifth, these regions of the genome are sheltered from recombination, and as a consequence transposons accumulate and foment genetic

rearrangements [46]. Hence, the *MAT* locus of *C. neoformans* has characteristics mirroring both the homomorphic sex chromosomes in species such as the fish *Medaka* and the plant papaya [47] and heteromorphic sex chromosomes.

The details of the evolutionary dynamics of the *MAT* loci of the species within the pathogenic *Cryptococcus* species complex are not yet clear. It is possible that these *MAT* loci have also undergone extensive gene loss and have reached an evolutionary static stage, like those observed in the human Y chromosome. Alternatively, they might have experienced rejuvenating turnover events such as those that have been observed in fishes and tree frogs. Additionally, because *C. neoformans* is haploid, any potential degeneration of the genes located within the *MAT* will be exposed to natural selection. This is similar to the situation in plants where haploid purifying selection helps to maintain genes located on the sex chromosomes.

Different from the two sexes that are observed in most multicellular organisms, some microbial species have more than two sexes/mating-types. For example, the model slime mold *Dictyostelium discoideum* has three mating types controlled by a single tri-allelic *MAT* locus [48]. Multiple mating-types are also maintained in ciliates such as *Tetrahymena* [49]. Additionally, hundreds to thousands of different mating-types exist in some mushroom fungi, such as *Coprinopsis cinerea* and *Schizophyllum commune* [50].

In Volvocine algae, both unicellular genera (e.g. *Chlamydomonas*) and multicellular genera (e.g. *Volvox*) exist. The unicellular species reproduce via equal-sized gametes (isogamy) generated by cells of *plus* and *minus* mating-types. The multicellular species *Volvox carteri* reproduces through sperm and egg (anisogamy) produced by morphologically differentiated male and female individuals [51,52]. Mating types in both unicellular and multicellular Volvocine algae are controlled by a single biallelic mating-type determining (*MT*) locus. However, there is a significant expansion in size and increased sequence divergence of the *MT* locus in the multicellular *Volvox*. This likely occurred via stepwise sequence addition into an ancestral *MT* locus to fashion what now appear to be bona fide sex chromosomes in *Volvox* [52]. In addition, the lower level of divergence observed at the *Chlamydomonas MT* locus indicates that these sex determining regions might have undergone one or multiple rounds of collapse/reformation. This example may be similar to the young sex chromosomes observed in European tree frogs [10].

Taken together, despite the vast evolutionary distances that separate complex multicellular metazoans from unicellular microorganisms, there are conserved features of the sex-determining regions across animals, plants, fungi, slime molds and algae. These sex-determining regions are called sex chromosomes in organisms that are anisogametic and with morphologically distinct sexes, and mating types in those that are isogametic with two morphologically similar individuals that engage in sexual reproduction. One way in which the trajectory for sex chromosomes and mating type loci may differ involves the degeneration of the Y chromosome in the sheltered state of an obligate diploid organism. But even in this case there may be opportunities for similar events to transpire in fungi. This may involve basidiomycetes that spend much of their life cycle as dikaryotic hyphae, or fungi that are either obligate diploids or in which the haploid state is fleeting and transient, like the gametes of multicellular animals. In summary, the study of simpler sex and mating type determining systems in both unicellular and multicellular microbes, as well as plants, pre-metazoans and diverse animals, will likely continue to reveal both shared and unique principles that underlie the fascinating diversity of sex determination systems and mechanisms that are central to sexual reproduction.

Conclusion

Although there are forces acting to preserve the human Y chromosome, it is nevertheless still faced with potentially destructive factors. These include a lack of meiotic recombination resulting in a lower efficiency of natural selection, and significantly reduced effective population size, rendering it prone to random genetic drift. The fate of the human Y chromosome lies in the balance between these preserving and destructive forces. Thus, even though it now appears that the human Y chromosome is here to stay, and likely for a long time to come, we cannot exclude the possibility that it may experience further degeneration. In addition, studies on the simpler *MAT* loci in unicellular organisms, such as fungi, algae, slime molds, and other protists will continue to provide additional insights into the evolution of the sex chromosomes in multicellular organisms.

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References

1. Ross MT, Grafham DV, Coffey AJ, Scherer S, et al. The DNA sequence of the human X chromosome. *Nature*. 2005; 434:325–37. [PubMed: 15772651]
2. Skaletsky H, Kuroda-Kawaguchi T, Minx PJ, Cordum HS, et al. The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. *Nature*. 2003; 423:825–37. [PubMed: 12815422]
3. Bachtrog D, Hom E, Wong K, Maside X, et al. Genomic degradation of a young Y chromosome in *Drosophila miranda*. *Genome Biology*. 2008; 9:R30. [PubMed: 18269752]
4. Bachtrog D. Adaptation shapes patterns of genome evolution on sexual and asexual chromosomes in *Drosophila*. *Nat Genet*. 2003; 34:215–9. [PubMed: 12754509]
5. Zhou Q, Wang J, Huang L, Nie W, et al. Neo-sex chromosomes in the black muntjac recapitulate incipient evolution of mammalian sex chromosomes. *Genome Biology*. 2008; 9:R98. [PubMed: 18554412]
6. Kaiser VB, Zhou Q, Bachtrog D. Nonrandom gene loss from the *Drosophila miranda* neo-Y chromosome. *Genome Biology and Evolution*. 2011; 3:1329–37. [PubMed: 21987387]
7. Bergero R, Charlesworth D. Preservation of the Y transcriptome in a 10-million-year-old plant sex chromosome system. *Curr Biol*. 2011; 21:1470–4. [PubMed: 21889891]
8. Chibalina MV, Filatov DA. Plant Y chromosome degeneration is retarded by haploid purifying selection. *Curr Biol*. 2011; 21:1475–9. [PubMed: 21889890]
9. Muyle A, Zemp N, Deschamps C, Mousset S, et al. Rapid de novo evolution of X chromosome dosage compensation in *Silene latifolia*, a plant with young sex chromosomes. *PLoS Biol*. 2012; 10:e1001308. [PubMed: 22529744]
10. Stöck M, Horn A, Grossen C, Lindtke D, et al. Ever-young sex chromosomes in European tree frogs. *PLoS Biol*. 2011; 9:e1001062. [PubMed: 21629756]
11. Kondo M, Nanda I, Hornung U, Schmid M, et al. Evolutionary origin of the medaka Y chromosome. *Curr Biol*. 2004; 14:1664–9. [PubMed: 15380069]
12. Ross JA, Urton JR, Boland J, Shapiro MD, et al. Turnover of sex chromosomes in the stickleback fishes (Gasterosteidae). *PLoS Genet*. 2009; 5:e1000391. [PubMed: 19229325]
13. Peichel CL, Ross JA, Matson CK, Dickson M, et al. The master sex-determination locus in threespine sticklebacks is on a nascent Y chromosome. *Curr Biol*. 2004; 14:1416–24. [PubMed: 15324658]
14. Benatti TR, Valicente FH, Aggarwal R, Zhao C, et al. A neo-sex chromosome that drives postzygotic sex determination in the Hessian fly (*Mayetiola destructor*). *Genetics*. 2010; 184:769–77. [PubMed: 20026681]
15. Pala I, Naurin S, Stervander M, Hasselquist D, et al. Evidence of a neo-sex chromosome in birds. *Heredity*. 2012; 108:264–72. [PubMed: 21897438]

16. Carvalho AB, Clark AG. Y chromosome of *D. pseudoobscura* is not homologous to the ancestral *Drosophila* Y. *Science*. 2005; 307:108–10. [PubMed: 15528405]
17. Kuroiwa A, Ishiguchi Y, Yamada F, Shintaro A, et al. The process of a Y-loss event in an XO/XO mammal, the Ryukyu spiny rat. *Chromosoma*. 2010; 119:519–26. [PubMed: 20443119]
18. Graves JAM. Sex chromosome specialization and degeneration in mammals. *Cell*. 2006; 124:901–14. [PubMed: 16530039]
19. Hughes JF, Skaletsky H, Pyntikova T, Graves TA, et al. Chimpanzee and human Y chromosomes are remarkably divergent in structure and gene content. *Nature*. 2010; 463:536–9. [PubMed: 20072128]
20. Hughes JF, Skaletsky H, Brown LG, Pyntikova T, et al. Strict evolutionary conservation followed rapid gene loss on human and rhesus Y chromosomes. *Nature*. 2012; 483:82–6. [PubMed: 22367542]
21. Hughes JF, Skaletsky H, Pyntikova T, Minx PJ, et al. Conservation of Y-linked genes during human evolution revealed by comparative sequencing in chimpanzee. *Nature*. 2005; 437:100–3. [PubMed: 16136134]
22. Rozen S, Marszalek JD, Alagappan RK, Skaletsky H, et al. Remarkably little variation in proteins encoded by the Y chromosome's single-copy genes, implying effective purifying selection. *The American Journal of Human Genetics*. 2009; 85:923–8.
23. Rozen S, Skaletsky H, Marszalek JD, Minx PJ, et al. Abundant gene conversion between arms of palindromes in human and ape Y chromosomes. *Nature*. 2003; 423:873–6. [PubMed: 12815433]
24. Shi J, Wolf SE, Burke JM, Presting GG, et al. Widespread gene conversion in centromere cores. *PLoS Biol*. 2010; 8:e1000327. [PubMed: 20231874]
25. Sun S, Hsueh Y-P, Heitman J. Gene conversion occurs within the mating-type locus of *Cryptococcus neoformans* during sexual reproduction. *PLoS Genet*. 2012; 8:e1002810. [PubMed: 22792079]
26. Galtier N, Piganeau G, Mouchiroud D, Duret L. GC-content evolution in mammalian genomes: the biased gene conversion hypothesis. *Genetics*. 2001; 159:907–11. [PubMed: 11693127]
27. Galtier N, Bazin E, Bierné N. GC-biased segregation of noncoding polymorphisms in *Drosophila*. *Genetics*. 2006; 172:221–8. [PubMed: 16157668]
28. Escobar JS, Glémin S, Galtier N. GC-biased gene conversion impacts ribosomal DNA evolution in vertebrates, angiosperms, and other eukaryotes. *Mol Biol Evol*. 2011; 28:2561–75. [PubMed: 21444650]
29. Galtier N. Recombination, GC-content and the human pseudoautosomal boundary paradox. *Trends Genet*. 2004; 20:347–9. [PubMed: 15262406]
30. Birky CW Jr, Walsh JB. Biased gene conversion, copy number, and apparent mutation rate differences within chloroplast and bacterial genomes. *Genetics*. 1992; 130:677–83. [PubMed: 1551584]
31. Khakhlova O, Bock R. Elimination of deleterious mutations in plastid genomes by gene conversion. *The Plant Journal*. 2006; 46:85–94. [PubMed: 16553897]
32. Connallon T, Clark AG. Gene duplication, gene conversion and the evolution of the Y chromosome. *Genetics*. 2010; 186:277–86. [PubMed: 20551442]
33. Marais GAB, Campos PRA, Gordo I. Can intra-Y gene conversion oppose the degeneration of the human Y chromosome? A simulation study. *Genome Biology and Evolution*. 2010; 2:347–57. [PubMed: 20624739]
34. Gordon JL, Armisén D, Proux-Wéra E, ÓhÉigeartaigh SS, et al. Evolutionary erosion of yeast sex chromosomes by mating-type switching accidents. *Proceedings of the National Academy of Sciences*. 2011; 108:20024–9.
35. de Clare M, Pir P, Oliver S. Haploinsufficiency and the sex chromosomes from yeasts to humans. *BMC Biol*. 2011; 9:15. [PubMed: 21356089]
36. Lee SC, Corradi N, Byrnes EJ 3rd, Torres-Martinez S, et al. Microsporidia evolved from ancestral sexual fungi. *Curr Biol*. 2008; 18:1675–9. [PubMed: 18976912]
37. Bakkeren G, Kronstad JW. Linkage of mating-type loci distinguishes bipolar from tetrapolar mating in basidiomycetous smut fungi. *Proc Natl Acad Sci USA*. 1994; 91:7085–9. [PubMed: 7913746]

38. Lee N, Bakkeren G, Wong K, Sherwood JE, et al. The mating-type and pathogenicity locus of the fungus *Ustilago hordei* spans a 500-kb region. *Proc Natl Acad Sci, USA*. 1999; 96:15026–31. [PubMed: 10611332]
39. D'Souza CA, Kronstad JW, Taylor G, Warren R, et al. Genome variation in *Cryptococcus gattii*, an emerging pathogen of immunocompetent hosts. *mBio*. 2011; 2:e00342–10. [PubMed: 21304167]
40. Loftus BJ, Fung E, Roncaglia P, Rowley D, et al. The genome of the basidiomycetous yeast and human pathogen *Cryptococcus neoformans*. *Science*. 2005; 307:1321–4. [PubMed: 15653466]
41. Lin X, Hull CM, Heitman J. Sexual reproduction between partners of the same mating type in *Cryptococcus neoformans*. *Nature*. 2005; 434:1017–21. [PubMed: 15846346]
42. Metin B, Findley K, Heitman J. The mating type locus (*MAT*) and sexual reproduction of *Cryptococcus heveanensis*: insights into the evolution of sex and sex-determining chromosomal regions in fungi. *PLoS Genet*. 2010; 6:e10000961.
43. Findley K, Sun S, Fraser JA, Hsueh Y-P, et al. Discovery of a modified tetrapolar sexual cycle in *Cryptococcus amyloletus* and the evolution of *MAT* in the *Cryptococcus* species complex. *PLoS Genet*. 2012; 8:e1002528. [PubMed: 22359516]
44. XU J, Vilgalys R, Mitchell TG. Multiple gene genealogies reveal recent dispersion and hybridization in the human pathogenic fungus *Cryptococcus neoformans*. *Mol Ecol*. 2000; 9:1471–81. [PubMed: 11050543]
45. Sun S, Hsueh Y-P, Heitman J. Gene conversion occurs within the mating-type locus of *Cryptococcus neoformans* during sexual reproduction. *PLoS Genet*. in press.
46. Fraser JA, Diezmann S, Subaran RL, Allen A, et al. Convergent evolution of chromosomal sex-determining regions in the animal and fungal kingdoms. *PLoS Biol*. 2004; 2:e384. [PubMed: 15538538]
47. Fraser JA, Heitman J. Chromosomal sex-determining regions in animals, plants and fungi. *Current Opinion in Genetics and Development*. 2005; 15:645–51. [PubMed: 16182521]
48. Bloomfield G, Skelton J, Ivens A, Tanaka Y, et al. Sex determination in the social amoeba *Dictyostelium discoideum*. *Science*. 2010; 330:1533–6. [PubMed: 21148389]
49. Phadke SS, Zufall RA. Rapid diversification of mating systems in ciliates. *Biol J Linn Soc*. 2009; 98:187–97.
50. Heitman, J.; Kronstad, JW.; Taylor, JW.; Casselton, LA. Sex in fungi: Molecular determination and evolutionary implications. Washington, D.C: ASM Press; 2007.
51. Umen JG. Evolution of sex and mating loci: An expanded view from Volvocine algae. *Curr Opin Microbiol*. 2011; 14:634–41. [PubMed: 22035946]
52. Ferris P, Olson BJSC, De Hoff PL, Douglass S, et al. Evolution of an expanded sex-determining locus in *Volvox*. *Science*. 2010; 328:351–4. [PubMed: 20395508]
53. Griffin D. Is the Y chromosome disappearing?—Both sides of the argument. *Chromosome Research*. 2012; 20:35–45. [PubMed: 22083302]

Figure 1. Evolutionary trajectory of the non-recombining sex chromosome (using the human Y chromosome as an example)

The neo-X and Y chromosomes appeared about 160 million years ago (MYA), with each possessing about 1600 genes. While the X chromosome has not experienced significant degeneration, the Y chromosome has degraded significantly over time. This degradation is mainly due to the reduced population size that renders the Y chromosome prone to genetic drift, as well as reduces the efficiency of natural selection. The lack of natural selection was further enforced by the fact that meiotic recombination is suppressed across the majority of the Y chromosome (the black down arrows). On the other hand, there are factors that have been acting to counteract the degenerative forces and maintain the gene content of the Y chromosome. These include strong purifying selection, as well as gene conversions among copies of the duplicated genes that can homogenize the copies and maintain their sequence integrity (the green up arrows). The future of the human Y chromosome is still debated. The Y could still be on its way to complete degeneration (the black dashed line). Or it may be that the destructive and positive forces have reached equilibrium and the Y chromosome has achieved a stable status (the green dashed line). The red dashed line illustrates one of the possible evolutionary trajectories that the Y chromosome could have taken – a simple linear degradation. The degeneration of the Y chromosome could also be exponential, and occurred faster at the beginning and then slowed gradually. Another possible mode of degeneration is through a multi-stage process, taking into account a later addition of genes onto the human Y chromosome that occurred ~100 MYA (see [18,53]).