



HAL
open science

Why do sex chromosomes progressively lose recombination?

Paul Jay, Daniel Jeffries, Fanny E Hartmann, Amandine Véber, Tatiana Giraud

► **To cite this version:**

Paul Jay, Daniel Jeffries, Fanny E Hartmann, Amandine Véber, Tatiana Giraud. Why do sex chromosomes progressively lose recombination?. Trends in Genetics, In press, 10.1016/j.tig.2024.03.005 . hal-04565142

HAL Id: hal-04565142

<https://hal.science/hal-04565142>

Submitted on 1 May 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1
2
3 **Why do sex chromosomes progressively lose recombination?**
4

5 Paul Jay^{1,2*}, Daniel Jeffries³, Fanny E. Hartmann², Amandine Véber⁴, Tatiana Giraud²

6 ¹Center for GeoGenetics, University of Copenhagen, Copenhagen, Denmark

7 ²Université Paris-Saclay, CNRS, AgroParisTech, Laboratoire Ecologie Systématique et Evolution, UMR 8079,
8 Bâtiment 680, 12 route RD128, 91190 Gif-sur-Yvette, France

9 ³Division of Evolutionary Ecology, Institute of Ecology and Evolution, University of Bern, 3012 Bern, Switzerland.

10 ⁴ Université Paris Cité, CNRS, MAP5, F-75006 Paris

11 *corresponding author

12 ORCID Numbers:

13 TG : 0000-0002-2685-6478

14 PJ: 0000-0001-5979-1263

15 DJ: 0000-0003-1701-3978

16 FEH: 0000-0002-9365-4008

17 AV: 0000-0003-4464-015X

18 **Abstract**

19 Progressive recombination loss is a common feature of sex chromosomes. Yet, the evolutionary
20 drivers of this phenomenon remain a mystery. For decades, differences in trait optima between
21 sexes (sexual antagonism) has been the favoured hypothesis, but convincing evidence is lacking.
22 Recent years have seen a surge of alternative hypotheses to explain progressive extensions and
23 maintenance of recombination suppression: neutral accumulation of sequence divergence, selection
24 of non-recombining fragments with fewer deleterious mutations than average, sheltering of
25 recessive deleterious mutations by linkage to heterozygous alleles, early evolution of dosage
26 compensation and constraints on recombination restoration. Here, we explain these recent
27 hypotheses and dissect their assumptions, mechanisms and predictions. We also review empirical
28 studies that have brought support to the various hypotheses.

29 **Keywords:** sex chromosomes, mating-type chromosomes, recombination suppression, evolutionary
30 strata, supergenes, inversion

31 **Main text**

32 **Why does recombination suppression progressively extend on sex chromosomes?**

33 The loss of recombination on sex chromosomes is an enigma that has fascinated evolutionary
34 biologists for decades. Recombination indeed allows efficient selection and the purging of
35 deleterious mutations [1,2]. Recombination suppression therefore leads to the accumulation of
36 deleterious mutations and thus the degeneration of sex chromosomes [3,4], which can account for
37 diseases and the shorter life-span of XY males in many species, including humans [5,6]. Despite
38 these long-term detrimental effects, progressive extensions of recombination suppression with time
39 has been documented on sex chromosomes in many plants and animals [7-17]. However, the
40 question of why recombination suppression progressively extends beyond genes involved in sex
41 determination is still unresolved [18,19].

42 The most widely accepted hypothesis to explain progressive extensions of recombination
43 suppression on sex chromosomes has long been **sexual antagonism** (see Glossary) [18,20-23].
44 Linking **sexually antagonistic** genes to the sex-determining loci could be beneficial, because it
45 ensures, for example, that only males express male-beneficial, female-deleterious alleles. Though
46 appealing, little evidence has been found that supports this hypothesis [24-29]. Furthermore,
47 progressive extensions of recombination suppression have recently been documented around
48 autosomal **supergenes** [30,31] (see Glossary), as well as on mating-type chromosomes in fungi that
49 lack differentiated sexes and phenotypic differences between **mating types** [32-34] (See Glossary).
50 Additionally, many species with strong sexual dimorphism do not show progressive extensions of
51 recombination suppression on sex chromosomes [15,35-38]. Recently, several new hypotheses have
52 been proposed, which do not invoke **sexual antagonism**, but instead are based on non-selective
53 processes or on the presence of deleterious mutations in genomes [39-43]. Here, we synthesise the
54 hypotheses developed to explain the evolution of recombination suppression, either in a single step
55 or progressively, and in particular the ones we developed [39,41]. We also identify predictions of
56 the different hypotheses explaining progressive extensions of recombination, evaluate empirical
57 evidence, and suggest directions for future empirical research. We focus on the evolutionary causes
58 of recombination suppression and discuss the proximate mechanisms in Box 1.

59 **I- Evolutionary mechanisms explaining recombination suppression around sex-determining**
60 **loci but no progressive extension**

61 Various hypotheses have been developed for explaining recombination suppression between the
62 genes involved in sex- or **mating-type** determination, which has been extensively reviewed [19,25].
63 These hypotheses are based on the emergence of dioecy via male-sterility and female-sterility genes
64 [44-46], the proper key and lock functions in mating compatibility [32,45,47] or meiotic drive [44].
65 Other hypotheses can explain recombination suppression beyond sex-determining genes but not
66 progressive extension; these include the pre-existence of regions with low rates of recombination
67 [26,48-52] and the promotion of particular segregation patterns at meiosis [53]. Below we focus on
68 the evolutionary mechanisms driving progressive recombination suppression, either gradually or
69 through stair-like **evolutionary strata** (see Glossary).

70 **II- Evolutionary mechanisms explaining progressive loss of recombination**

71 Understanding the evolutionary causes of progressive recombination suppression requires
72 recognizing three distinct stages: i) the initial selective advantage of non-recombining fragments
73 that makes them rise in frequency, ii) the conditions that allow them to reach fixation despite their
74 captured or accumulated recessive deleterious mutations, iii) the maintenance of non-recombining
75 fragments on sex chromosomes despite degeneration that results from recombination suppression.
76 Understanding progressive recombination suppression around sex- and **mating-type** determining
77 genes, and other heterozygous **supergenes**, also requires elucidating why this does not occur
78 elsewhere in genomes.

79

80 **i) Evolutionary mechanisms allowing non-recombining fragments to rise in frequency**

81 **Directly beneficial non-recombining fragment*

82 Non-recombining fragments can be directly beneficial, for example if inversion breakpoints
83 generate beneficial mutations by changing gene expression, generating duplications, chimeric genes
84 or deletions [54]. This has been suggested in the case of autosomal **supergenes** [54-56] and could
85 be applicable to **evolutionary strata** on sex chromosomes [42]. Indeed, if a beneficial inversion
86 overlaps with the existing non-recombining region in a sex chromosome, it can only fix on the sex
87 chromosome in which it appeared (X or Y). This will maintain the inversion at the heterozygous
88 state, thereby expanding the non-recombining region between the two sex chromosomes.

89 **Beneficial allelic combinations: sexual antagonism and local adaptation*

90 The first proposed selective advantage of non-recombining fragments on sex chromosomes is the
91 linkage of **sexually antagonistic** loci to sex-determining genes, so that, for example, only males
92 carry alleles that are only beneficial to males [57,58] (Figure 1a). Theoretical models have however
93 suggested that **sexual antagonism** may be better solved through the differential expression of
94 autosomal genes [59].

95 Another well-known advantage of recombination suppression is for promoting local adaptation, i.e.
96 for maintaining beneficial allelic combinations in different environments in the face of gene flow
97 [55,60]. Theoretical models suggested that X-like chromosomes (i.e. sex chromosomes recombining
98 in one sex) may disproportionately contribute to local adaptation because selection is more efficient
99 [61]. Such non-recombining fragments on X-like chromosomes would suppress recombination with
100 Y-like chromosomes.

101 **Selection for less-loaded or “lucky” fragments*

102 Another selective advantage of non-recombining fragments can be that, by chance, they occur on a
103 chromosomal segment with fewer deleterious mutations than the population average in this genomic
104 region [62], which occurs in nearly half of reasonably large, random inversions [39]. These “less-
105 **loaded**” [39] (see Glossary) or “lucky” fragments [40] have a direct intrinsic fitness advantage and
106 should therefore increase in frequency, in autosomes or in sex chromosomes (Figure 1b).

107 **Initial sheltering advantage under inbreeding or automixis*

108 Non-recombining fragments linked to a **permanently heterozygous allele** (see Glossary) could be
109 favoured due to the **sheltering** (see Glossary) of their partially recessive deleterious mutations (Box
110 2). Indeed, the linkage to a **permanently heterozygous allele** can maintain recessive deleterious
111 mutations in a heterozygous state, allowing the masking of their deleterious effects. However, such
112 sheltering is only possible if there is **linkage disequilibrium** (see Glossary) between loci with
113 recessive deleterious mutations and the **permanently heterozygous allele**. Such **linkage**
114 **disequilibrium** indeed means that some deleterious mutations can be more frequent on the
115 **permanently heterozygous**, Y-like chromosome than on the X, so that their effect can be masked
116 by functional copies on the X-like chromosome (Figure 1c, Boxes 2 and 3). The **linkage**
117 **disequilibrium** can be generated by partial inbreeding, drift [63] or by particular mating systems,
118 such as **automixis** (see Glossary) [64,65].

119 **Neutral hypotheses*

120 Neutral inversions (i.e., with selective effects weaker than genetic drift) linked to the sex-
121 determining gene could rise in frequency via genetic drift more often on sex chromosomes than on
122 autosomes, because of the smaller effective population size of sex chromosomes [24,57,66-69]. A
123 recent model [41] simulated neutral point mutations accumulating at the margin of the non-
124 recombining region, increasing sequence divergence between sex chromosomes. Provided that
125 sequence divergence reduces local recombination rates, this can, in turn, increase genetic linkage
126 with the non-recombining region [41] and subsequently lead to further accumulation of sequence
127 divergence (Figure 1d). This self-reinforcing neutral process could progressively extend the non-
128 recombining region. The enrichment of transposable elements in non-recombining regions could

129 also promote the progressive extension of the non-recombining region as these elements often carry
130 silencing marks with a recombination-suppressing effect (e.g. methylation) [68,70,71], and the
131 silencing marks can extend to nearby regions [72].

132
133 **ii) Fixation of non-recombining fragments despite mutation load**

134 The mechanisms reviewed above can explain the rise in frequency of non-recombining fragments,
135 and several can apply to autosomes or X-like chromosomes. However, any relatively large non-
136 recombining genomic segment is likely to include partially recessive deleterious mutations (i.e.
137 **mutation load**; see Glossary). When such **loaded** autosomal or X-linked non-recombining
138 fragments spread in a population, they will increasingly occur in a homozygous state, which will
139 expose their recessive deleterious mutations. This will stop their spread, regardless of the reason
140 why they initially increased in frequency. Therefore, non-recombining fragments carrying
141 deleterious recessive mutations on autosomes and X-like chromosomes will be unlikely to fix,
142 unless they benefit from a strong fitness advantage compensating their **mutation load**
143 [39,42,62,73].

144 In contrast, non-recombining fragments that capture a **permanently heterozygous allele** (e.g. a Y-
145 like sex-determining allele) will never be homozygous, even when becoming frequent [31,74]. By
146 becoming linked to a **permanently heterozygous locus**, the deleterious recessive mutations on the
147 non-recombining fragments become **sheltered** (Figure 1e). As above, this **sheltering** effect requires
148 **linkage disequilibrium** between these deleterious mutations and the **permanently heterozygous**
149 **allele**. Here, linkage disequilibrium is generated by the increase in frequency of the non-
150 recombining fragment that captured both the **permanently heterozygous allele** and the deleterious
151 mutations (Box 2). This key phenomenon has been overlooked in recent debates about the
152 sheltering hypothesis [43,75]. For example, in the case of a **loaded** non-recombining fragment on a
153 Y chromosome having risen in frequency (regardless of the reason why), the frequency of the
154 captured deleterious mutations will be much higher on the Y than on the X chromosome
155 (constituting **linkage disequilibrium**); consequently, these mutations are sheltered. Such **sheltering**
156 allows non-recombining fragments to reach fixation on Y-like chromosomes despite carrying
157 recessive deleterious mutations [39,43]. This **sheltering** effect has been modelled for the lower-load
158 advantage [39], but can apply to other selective advantages and neutral hypotheses. The
159 **sheltering** effect during the fixation phase on Y-like chromosomes could thus explain why
160 recombination suppression extends on sex chromosomes and not on autosomes.

161 The fitness of non-recombining fragments may erode with time during the fixation phase, as they
162 accumulate deleterious mutations because of recombination suppression [39,43,76,77]. To reach

163 fixation, their fitness needs to remain above average until fixation. Simulations showed that the
164 accumulation of deleterious mutations during the fixation phase did not prevent many non-
165 recombining fragments from fixing on Y-like sex chromosomes under a wide range of parameters
166 [39,40,43]. New, partially recessive deleterious mutations accumulating during fixation of a non-
167 recombining fragment on a Y-like chromosome will also be **sheltered**, as they are unlikely to also
168 occur on the X-like chromosome.

169

170 **iii) Long-term persistence of non-recombining regions**

171 Once non-recombining fragments are fixed on sex chromosomes, they accumulate further
172 deleterious mutations, in particular because recombination suppression renders selection less
173 efficient [3]. Selection could therefore favor recombination restoration when the **mutation load** of
174 non-recombining fragments becomes higher than their initial selective advantage (Figure 1f).

175 To explain the persistence of non-recombining regions despite accumulated **mutation load**, a first
176 hypothesis postulates that rearrangements accumulate more rapidly in these regions than deleterious
177 mutations. When non-recombining regions have accumulated a mutation load outweighing their
178 selective advantage, the chaos of rearrangements they carry would render recombination restoration
179 very difficult [39]. This is called the “constraint” hypothesis (Figures 1g and 2), as recombination
180 restoration is prevented by rearrangements constraining the possibility of regenerating a collinear,
181 recombinant chromosome. Indeed, if multiple overlapping or nested inversions accumulate
182 following recombination suppression (as often observed [33,78-83]), the only way of restoring a
183 fully recombining chromosome is that new inversions occur at the same breakpoints and in the
184 same reverse order as the initial inversions occurred [39]. Nested or overlapping inversions can re-
185 align a fraction of the genes, but some other genes will remain shuffled. This hypothesis does not
186 predict that non-recombining sex chromosomes are everlasting, only that evolutionary strata persist
187 long enough to be observed. Once sex chromosomes are too much degenerated, there could be sex
188 chromosome turnover, i.e., the sex-determining genes could move to an autosome, as reported in
189 several organisms [84].

190 A second hypothesis, called the “regulatory hypothesis”, postulates that there is no constraint on
191 recombination restoration, but that **dosage compensation** (see Glossary) evolves very rapidly and
192 renders recombination restoration deleterious (Figure 1h). In this hypothesis, inversions that have
193 accumulated following recombination suppression can be reversed relatively easily by subsequent
194 inversions reusing the same breakpoints and in the same order. However, **dosage compensation**
195 evolves early [40,85]: degenerated genes on the Y-like sex chromosome become silenced owing to
196 a decrease in the strength of their cis-regulators (Figure 1h), which is very rapidly compensated for

197 by changes in their pre-existing gene-specific, sex-specific **trans-acting gene expression**
198 **regulators** (see Glossary) maintaining near-optimal expression in both sexes. Under these
199 conditions, recombination restoration is selected against as it results in a mismatch between
200 expression regulators, generating suboptimal gene expression [40]. The recent debate opposing
201 the constraint and regulatory hypotheses [86] stems from a lack of understanding that the constraint
202 hypothesis does not imply a lack of dosage compensation evolution in the long term; the constraint
203 hypothesis only postulates that the maintenance of non-recombining regions does not require *early*
204 evolution of dosage compensation.

205 A third hypothesis to explain the persistence of evolutionary strata could be that **sexually**
206 **antagonistic** mutations accumulate following recombination suppression on sex chromosomes [83],
207 conferring an advantage stronger than the accumulating **mutation load**, therefore selecting against
208 recombination restoration.

209 **III- Predictions of the recent hypotheses and available evidence**

210 Below we highlight predictions for the various hypotheses explaining the progressive extension of
211 recombination suppression as well as available evidence. Additional predictions can be made,
212 for example on the frequency of sex chromosome-autosome fusions, the fitness decrease of the
213 **heterogametic** sex (see Glossary), the footprints of selective sweeps or the impact of effective
214 population size, but they currently lack theoretical investigations.

215 *Sexually antagonistic gene enrichment in Y-like chromosomes*

216 The **sexual antagonism** hypothesis predicts that non-recombining regions should be enriched in
217 **sexually antagonistic** genes, as this would be the way to resolve **sexual antagonism**. Such a
218 pattern has however very rarely been documented despite being intensively investigated [24,28,87-
219 90]. In the rare cases where sex chromosomes appeared enriched in **sexually antagonistic** genes,
220 such as in male coloration genes on the Y chromosome in a guppy [91], low recombination rates on
221 the Y chromosome may have favored the subsequent establishment of **sexually antagonistic** genes
222 [50,92,93].

223 *Correlation between sexual dimorphism level and number of evolutionary strata*

224 A related prediction of the **sexual antagonism** theory is that a higher number of **evolutionary**
225 **strata** and larger non-recombining regions (considering size before degeneration) should occur in
226 species with stronger sexual dimorphism. However, **sexually antagonistic** genes can accumulate on
227 sex chromosomes after recombination suppression [83], which could lead to a correlation between

228 non-recombining region size and sexual dimorphism level. In contrast, the absence of such a
229 correlation contradicts the **sexual antagonism** hypothesis, provided that the sexual dimorphism
230 level was accurately assessed. Some comparative studies found significant positive correlations
231 between non-recombining region size and dimorphism [92,94], while others found none [81]. In
232 particular, some species display monomorphic sex chromosomes despite sexual dimorphism [35-
233 37], and others heteromorphic sex chromosomes despite low dimorphism levels [94]. In addition,
234 the existence of multiple **evolutionary strata** on **mating-type** chromosomes in a variety of fungi
235 [33,53,79,95,96], despite the absence of gamete dimorphism and of other types of antagonistic
236 selection [34], shows that **sexual antagonism** is not required for the evolution of progressive
237 recombination suppression.

238

239 *Mating system*

240 The initial **sheltering** advantage hypothesis predicts the existence of **evolutionary strata** only in
241 species with automictic or partially inbreeding mating systems [64,97]. Progressive recombination
242 suppression has been reported in inbreeding termites [98,99] and in many automictic fungi
243 [53,95,96,100-102] (Figure 3). However, **evolutionary strata** also occur in sex chromosomes of
244 many species with random mating [7,19,22], so that other mechanisms should be able to generate
245 **evolutionary strata**.

246 *Lack of recombination suppression around multi-allelic self-incompatibility loci*

247 The constraint hypothesis may predict that the long-term persistence of non-recombining regions
248 could be more challenging in multi-allelic systems, such as plant self-incompatibility loci. Indeed,
249 when more than two alleles are present at self-incompatibility loci, some alleles can be lost. Alleles
250 around which recombination suppression has evolved could thus be lost once they have
251 accumulated too many deleterious mutations [39]. In contrast, they could persist under the
252 hypotheses postulating that they harbor strong intrinsic advantage. The persistence of non-
253 recombining fragments via **dosage compensation** may also be more challenging around multi-
254 allelic loci, as **dosage compensation** should depend on the expression level of the alternative allele
255 and there are many different ones at multi-allelic loci. These predictions need theoretical
256 investigations, but data so far do suggest lack of recombination suppression extension beyond
257 multi-allelic self-incompatibility loci in plants [103] and multi-allelic mating-type loci in fungi
258 (Figure 3).

259 *Ploidy in the main phase of life cycles*

260 A prediction of the theories involving deleterious mutations is that only organisms with extended
261 diploid or **dikaryotic** (see Glossary) phases in their life cycles should display progressive
262 recombination suppression, because i) haploid life cycles more efficiently purge them [104] and/or
263 ii) only diploid or **dikaryotic** phases can shelter recessive deleterious mutations. This prediction of
264 **evolutionary strata** being present only in diploid/**dikaryotic** organisms also holds for the
265 regulatory hypothesis [40], because **dosage compensation** can only evolve when cells carry two
266 different alleles. In contrast, **sexual antagonism** and neutral processes could promote
267 recombination suppression in organisms with predominantly haploid life cycles [105]. In fungi,
268 **evolutionary strata** have been observed only in **dikaryotic** species (Figure 3). Among
269 ascomycetes, that are usually haploid during most of their life cycle, a **dikaryotic** main phase has
270 evolved repeatedly, and has been found systematically associated with extension of recombination
271 suppression around **mating-type** loci [32,53,101,102] (Figure 3), in contrast to haploid ascomycetes
272 [106,107]. Bryophytes and algae could allow investigating the impact of the diploid phase length on
273 the number of **evolutionary strata** [17,108-112]. Brown algae with long haploid phases in fact
274 seem to lack **evolutionary strata** on their sex chromosomes [109,110]. In some green algae,
275 however, mating-type or sex chromosomes seem to display strata-like patterns despite a prolonged
276 haploid phase [111,113].

277 *Mutation rate and their fitness effect*

278 The lower-**load** advantage and the fixation-**sheltering** hypotheses predict more **evolutionary strata**
279 when the **mutation load** is higher [39], and therefore for higher rates of deleterious mutations and
280 more deleterious effects [114]. The neutral hypothesis predicts expansions of the non-recombining
281 region when neutral mutation rates are high [41]. The neutral/deleterious mutation rate should not
282 impact the number of **evolutionary strata** for other hypotheses, while the rate of **sexually**
283 **antagonistic** mutations may have an effect under the **sexual antagonism** hypothesis. New
284 sequencing and computational methods [115] should be able to provide estimates of mutation rates
285 and distribution of mutation fitness effects across a wide variety of organisms to test the existence
286 of a correlation with the number of **evolutionary strata** [116].

287 *Overdominance in young evolutionary strata*

288 The various theories based on deleterious mutation **sheltering** (Box 2) predict that, because of their
289 recessive **mutation load**, non-recombining fragments should often be **overdominant** (see
290 Glossary). **Overdominance** has been documented in several **supergenes**, for example in butterflies,
291 zebra finches and ants [31,117,118]. In order to detect recessive deleterious mutations that would
292 be a cause and not only a consequence of recombination suppression, experimental investigation of

293 the **overdominance** of non-recombining fragments should be conducted on very young
294 **evolutionary strata**. **Overdominance** could be tested, for example, by comparing the growth, as a
295 proxy of fitness, in fungi that carry young evolutionary strata and can be cultivated either as haploid
296 or dikaryotic mycelia.

297 *Gradual versus stair-like pattern of recombination cessation*

298 Patterns of gradual recombination suppression, as opposed to stair-like patterns, would support
299 neutral rather than adaptive processes. Indeed, very small non-recombining fragments are less likely
300 to capture haplotypes with a selective advantage compared to large non-recombining fragments, so
301 that recombination suppression involving small steps (yielding an apparently continuous
302 progressive extension) is likely generated by neutral processes [41]. Patterns of discontinuous strata
303 (stair-like) have been reported in a wide range of organisms, from plants and animals to fungi
304 [22,32,33,53,79,83,119-124]. Although more rarely, cases of more continuous shifts in the pseudo-
305 autosomal boundaries have been documented [49,125-128]. Assessing whether the divergence
306 pattern is discrete or gradual is challenging but change-point analyses and high-quality genome
307 assemblies provide valuable insights [129,130].

308 *Relative rates of rearrangements versus degeneration following recombination suppression*

309 The constraint hypothesis explaining the long-term persistence of non-recombining regions predicts
310 that inversions or other rearrangements occur more rapidly than the fitness decrease due to the
311 accumulation of deleterious mutations, so that multiple overlapping rearrangements completely
312 reshuffle gene order before degeneration is strong. Data in anther-smut fungi, with dozens of
313 independent events of recombination suppression of different ages, show that rearrangements within
314 non-recombining regions become chaotic before they accumulate non-synonymous substitutions or
315 suboptimal codon usage [4,33,79,95,131] (Figure 2). In the plant *Rumex hastatulus* too, extensive
316 rearrangements occurred on the sex chromosome before any gene loss or transposable element
317 accumulation [132]. With such a rapid accumulation of overlapping rearrangements, occurring
318 before strong degeneration, it seems extremely unlikely that recombination could be restored. This
319 would indeed require reverting inversions by subsequent inversions reusing the same breakpoints,
320 in the same order as they occurred. Only two cases of such inversion reversions have been
321 documented in the extensively studied *Drosophila melanogaster* [133]. For reversions to be
322 possible, the number of possible inversion breakpoints should be limited along genomes [39]. The
323 chaos of rearrangements in fungal **mating-type** chromosomes [33,78-80] and in Y chromosomes
324 [81-83], and a study on inversion polymorphism in humans [134], show in contrast that the number
325 of possible inversion breakpoints is high. However, we need data on inversion rates and their

326 breakpoints, for example by analysing progenies and populations with long-read sequencing.

327 It has been argued that the occurrence of sex chromosome turnovers would be a way to restore
328 recombination of rearranged, degenerated sex chromosomes [86], and that this possibility meant
329 that the constraint hypothesis could not explain long-term persistence of recombination suppression.
330 However, sex-chromosome turnovers do not contradict the constraint hypothesis (see above) [135]:
331 they may suggest, in contrast, that evolutionary strata have persisted long enough in populations to
332 degenerate, without early dosage compensation. Furthermore, sex chromosome turnovers likely
333 cannot occur in UV systems or mating-type chromosomes, in which the two chromosomes are non-
334 recombining and therefore degenerate: there is no X-like recombining chromosome that retains all
335 its functional genes and can become an autosome.

336 *More frequent inversions on sex chromosomes than on recombining chromosomes*

337 The local adaptation hypothesis predicts more frequent inversions on X-like chromosomes
338 (recombining in one sex) than on autosomes [61,136]. Because both chromosomes are non-
339 recombining in UV systems and mating-type chromosomes, this mechanism may not be able to
340 generate strata in these systems, which could allow testing this hypothesis.

341 The theories involving **sheltering** (Box2) predict more frequent inversions on Y-like chromosomes
342 than on autosomes or X-like chromosomes, due to the permanent heterozygosity of Y-like
343 chromosomes and the associated sheltering of captured deleterious recessive mutations [39].
344 Empirical data suggest that rearrangements fix more frequently on Y-like than on X-like
345 chromosomes or autosomes [33,79,82], although this needs to be formally tested, controlling for
346 possible confounding factors, such as increased mutation rates in males [137] and inversion
347 accumulation after recombination suppression.

348 *Gene-specific dosage compensation through cis- and trans-acting factors*

349 An assumption of the **dosage compensation** hypothesis for explaining the long-term persistence of
350 non-recombining regions is that the expression of many genes needs to be finely dosed, as the
351 hypothesis requires the rapid evolution of a complex **dosage compensation** mechanism [85]. A
352 prediction is therefore that dosage compensation should be observed in many genes and in all young
353 strata. **Dosage compensation** has been observed in several organisms, in particular mammals [138-
354 140]. However, the mere existence of **dosage compensation** is not a support for the regulatory
355 hypothesis, as it can evolve late in the degeneration process under all other hypotheses. Conversely,
356 the lack of **dosage compensation** in any species or strata would indicate that the regulatory
357 hypothesis cannot explain evolutionary strata, at least in such organisms. Many systems with

358 evolutionary strata exhibit incomplete or complete lack of **dosage compensation**, e.g. in birds,
359 snakes, fishes, turtles, frogs and plants [15,128,141 ,142 ,143-145]. Elucidating the temporal
360 dynamics of changes in gene expression compared to that of degeneration following recombination
361 suppression could help testing the regulatory hypothesis.

362 Another prediction of the regulatory hypothesis [40] is that numerous sex-specific *trans-acting*
363 **gene expression regulators** already exist before recombination suppression, constituting a kind of
364 sexual dimorphism. However, it remains to be assessed whether i) numerous *trans-acting* gene-
365 specific, sex-specific regulators occur along genomes and whether ii) they exist before the evolution
366 of recombination suppression. In mosquitoes for example, a single major regulator globally controls
367 **dosage compensation** on the whole X chromosome [146]. In mammals too, **dosage compensation**
368 occurs globally, by inactivating a whole X chromosome in each cell [147]. **Dosage compensation**
369 may be even more challenging to achieve in UV-like systems, as both sex or **mating-type**
370 chromosomes are permanently heterozygous, and so are expected to degenerate, with the most
371 degenerated allele being on one or the other chromosome depending on the gene. **Dosage**
372 **compensation** would therefore need to evolve on many genes with *trans-acting* gene-specific,
373 mating-type-specific regulators, and it remains to be assessed whether this can occur in nature. No
374 dosage compensation has actually been reported so far in UV systems or fungal mating-type
375 chromosomes, although this needs to be further explored.

376 **IV. Concluding Remarks and Future Perspectives**

377 In this paper, we aimed at summarising the hypotheses developed for explaining a long-standing
378 puzzle, the progressive evolution of recombination suppression in sex chromosomes and autosomal
379 **supergenes**. We have dissected predictions made by the different hypotheses and provided
380 examples of tests that could allow to disentangle hypotheses. However, data is currently too scarce
381 (see Outstanding Questions). Many of the predictions can indeed only be tested using comparative
382 studies with data available on many species, with diverse traits and large-scale population genomic
383 data. The Tree of Sex initiative (<https://treeofsex.sanger.ac.uk/>) aiming at building a database
384 compiling information on reproductive systems and associated data across eukaryotic life could be
385 highly useful to disentangle the hypotheses. The present paper provides clues on which traits need
386 to be informed in this database. Of course, the various proposed mechanisms are not mutually
387 exclusive and several may act in nature, in combination or in different organisms.

388 **Acknowledgements:**

389 This work was supported by the European Research Council (ERC) EvolSexChrom (832352) grant
390 to TG and a Human Frontier Science Program (HFSP) fellowship to PJ. We thank Michael E. Hood,
391 Tim Connallon, Alice Namias, Elise Lucotte and Ariel Offenstadt for comments on earlier versions
392 of this manuscript.

393 **Author contributions**

394 The manuscript has been written by TG and PJ and has been completed and edited by FEH, AV and
395 DJ. Figures have been made by PJ, TG and FEH. AV contributed to thinking about theories. .
396

397 **Declaration of Interests:** the authors declare no conflicts of interest

398 **Boxes:**

399 **Box 1: Proximate mechanisms influencing progressive recombination suppression**

400 Perhaps the simplest and most widely discussed proximate mechanism suppressing recombination
401 is via an inversion, whereby sequence collinearity is immediately broken over a large region
402 [55,148]. Crossing-over interference also occurs at the margin of inversions, mechanistically
403 preventing recombination much farther than around the inversion breakpoints [149,150]. Inversions
404 are often considered the primary proximal cause of the classic stair-like **evolutionary strata** effect
405 on sex chromosomes. However, inversions can also evolve as a consequence of recombination
406 suppression. Only a handful of studies have explicitly shown accordance between the boundaries of
407 **evolutionary strata** and breakpoints of inversions [83,151]; in contrast, multiple young
408 **evolutionary strata** are still collinear in fungi [32,53,79,80,96,102,152]. Experiments have further
409 shown that rearrangements cannot explain alone recombination suppression around **mating-type**
410 loci in a unicellular alga [111].

411 Most of the hypotheses reviewed in this paper can work with inversions as well as with other
412 proximal mechanisms. The insertion of transposable elements in regions of low recombination
413 could for instance result in the inhibition of recombination in surrounding regions, due to the host
414 silencing responses (e.g. DNA methylation or repressive chromatin) [68]. DNA methylation can
415 indeed lead to recombination suppression [68,71,72,153-157]. Proximate mechanisms of
416 recombination suppression could also be **trans-or cis-acting** recombination modifiers [158,159]
417 (see Glossary). The lack of recombination in the mating-type chromosomes of the yeast *Lachancea*
418 *kluuyveri* is due to the lack of recruitment of proteins responsible for double-strand breaks [160].
419 Sequence divergence accumulating in the low-recombination part near the sex-linked region could
420 also prevent recombination [41,161-163].

421 The proximal mechanisms of recombination suppression may however have evolutionary
422 consequences. Indeed, if the proximal mechanism of recombination suppression was an inversion,
423 recombination restoration would require an inversion reversion, i.e., the restoration of the original
424 sequence orientation via a second inversion reusing the same breakpoints. Restoring recombination
425 may be easier with other proximal mechanisms, unless rearrangements rapidly accumulate within
426 non-recombining regions. In addition, some evolutionary hypotheses are directly associated with
427 the proximal mechanism suppressing recombination, such as the hypotheses of beneficial inversion
428 breakpoints changing gene function or regulation, or the spread of transposable element silencing
429 marks suppressing recombination. Furthermore, the proximate causes can impact the likelihood of
430 non-recombining fragment fixation. For example, inversions can create lethal aneuploids (i.e. with

431 missing chromosomal parts), which can reduce fertility and thereby hinder inversion spread in
432 populations. Indeed, recombination within an inversion may lead to unbalanced gametes, with some
433 gametes having a large duplication and some others a large deletion. In such cases, the selective
434 advantage of non-recombining fragments must be higher than their intrinsic cost, which has been
435 taken into account only in some models [39].

436

437 **Box 2: Conditions allowing a sheltering advantage on sex chromosomes**

438 The **sheltering** of recessive deleterious mutations corresponds to the masking of non-optimal alleles
439 by functional ones owing to their maintenance in a heterozygous state. This occurs on sex
440 chromosomes due to the linkage, via recombination suppression, of deleterious mutations to a
441 **permanently heterozygous allele**, provided that these deleterious mutations are less frequent on
442 the alternative sex chromosome (i.e. that there is **linkage disequilibrium** between the sex-
443 determining locus and the deleterious mutations). Such **sheltering** can play a role in several phases
444 of sex-chromosome evolution.

445 **Sheltering** is most known to potentially act after the fixation of non-recombining fragments, as new
446 recessive deleterious mutations occurring in the non-recombining fragment are absent from the
447 homologous chromosome, therefore remaining heterozygous. This leads to the accumulation of
448 deleterious mutations, thereby contributing to the degeneration of sex chromosomes [2,77,164].

449 **Sheltering** can also favor the initial spread of non-recombining fragments, provided there is
450 **linkage disequilibrium** between deleterious recessive mutations and the sex-determining locus
451 [165]. Indeed, if a deleterious allele is more often on the Y than on the X chromosome,
452 recombination suppression linking the deleterious mutation and the heterozygous sex-determining
453 allele is advantageous, as it reduces the proportion of offspring homozygous for the recessive
454 deleterious mutation [64]. The initial **linkage disequilibrium** between deleterious mutations and
455 the heterozygous sex-determining allele can be due to drift or to non-random mating, e.g. under
456 **automixis** or inbreeding [64,97,166].

457 In large populations with random mating, even a small amount of recombination restores
458 linkage equilibrium between a locus with deleterious mutations and a **permanently heterozygous**
459 locus, preventing any initial gain due to **sheltering** [164,167]. In such populations, the **sheltering**
460 of deleterious mutations can nevertheless contribute to the fixation of beneficial non-recombining
461 fragments on Y-like sex chromosomes regardless of their initial advantage. Indeed, the rapid
462 increase in frequency of such non-recombining fragments generates an over-representation of their

463 deleterious mutations on the Y-like chromosome compared to its homologous chromosome, and the
464 lack of recombination maintains **linkage disequilibrium** (a phenomenon overlooked in recent
465 debates about the sheltering effect [43,75]). This leads to the **sheltering** of these deleterious
466 mutations, even in large populations and under random mating, allowing the fixation of these non-
467 recombining fragments on Y-like chromosomes despite their **mutation load** [39]. **Linkage**
468 **disequilibrium** will also exist between the sex-determining locus and new deleterious mutations
469 occurring in the non-recombining fragment during its fixation phase, also allowing their **sheltering**.
470

471 **Box 3: The different roles of deleterious mutations in recent models**

472 In several recent models aiming at explaining the progressive evolution of recombination
473 suppression in sex chromosomes [39,40,43], deleterious mutations play important roles. These
474 hypotheses are based on the observations that many deleterious mutations typically segregate in
475 genomes under mutation-selection equilibrium in diploid organisms [39,73,168-170]. In these
476 recent models, deleterious mutations play distinct roles in the three stages of the evolution of
477 suppressed recombination :

478 i) non-recombining fragments with fewer deleterious partially recessive mutations than average (i.e.
479 being “less-loaded” or “lucky”) have a higher fitness than the mean of the population and therefore
480 increase in frequency [39,40]; there is no **sheltering** effect at this initial stage;

481 ii) when non-recombining fragments increase in frequency thanks to their intrinsic advantage or
482 genetic drift, they increasingly occur at a homozygous state, which exposes their **mutation load** if
483 they carry recessive deleterious mutations. It is only when they also capture a **permanently**
484 **heterozygous** (Y-like) allele that they can continue increasing in frequency, as their recessive
485 deleterious mutations are then sheltered; non-recombining fragments with a recessive **mutation**
486 **load** are unlikely to fix on autosomes or X-like chromosomes [39]. Further deleterious mutations
487 may accumulate during the course of fixation [62], but a wide range of parameters still allow their
488 fixation [39,43,75]. Several points have not been always fully understood on this sheltering effect
489 [75]. First, the above sheltering effect only acts when non-recombining fragments are frequent, and
490 it needs to be studied separately from the “less-loaded” effect driving the initial increase in
491 frequency of non-recombining fragments. Second, neutral non-recombining fragments do not
492 constitute the right control to evaluate the sheltering effect, as this effect only *allows* non-
493 recombining fragments to fix *despite* their load. Therefore, this effect can only be studied by
494 comparing autosomes (where sheltering does not occur) to sex chromosomes (where sheltering

495 occurs), and *with* deleterious mutations segregating: the autosomes are the right controls for the
496 sheltering effect, as they carry the load but cannot be sheltered.

497 iii) After fixation on Y-like chromosomes, the non-recombining fragments will accumulate new
498 deleterious alleles due to recombination suppression, and will eventually become more **loaded** than
499 average, which should select for restoring recombination. The persistence of **evolutionary strata**
500 (at least long enough to be observed) can be due to constraints because too many overlapping
501 rearrangements have also accumulated, so that reversion to the initial, recombining state is unlikely
502 to occur [39], or because **dosage compensation** has already evolved, rendering recombination
503 restoration less advantageous [40], or because **sexually antagonistic** genes have also accumulated.
504 Under the constraint model, **evolutionary strata** eventually degenerate and fitness decreases, so
505 there can be sex-chromosome turn-over, i.e. the relocation of the sex-determining genes in a
506 different chromosome pair. This model could thus produce heteromorphic chromosomes and
507 maintain them long enough to be observed [39].

508 [Link to a 5 minute movie explaining the Jay et al. 2022 model:](https://www.youtube.com/watch?v=svFZB-n6VWA&ab_channel=PixVideosProductionCompany)

509 https://www.youtube.com/watch?v=svFZB-n6VWA&ab_channel=PixVideosProductionCompany
510

511 **Highlights**

512 - Explaining recombination suppression in sex chromosomes requires understanding i) the selective
513 advantage of non-recombining fragments, if any; ii) the reasons for their persistence following
514 degeneration; and iii) why these mechanisms occur specifically around sex-determining genes.

515 -Theories propose that recombination suppression can evolve due to neutral processes, **sexual**
516 **antagonism**, the capture of fewer deleterious mutations than average, or the **sheltering** of
517 deleterious mutations by **permanently heterozygous alleles**.

518 -Recombination suppression can be maintained by constraints due to overlapping chromosomal
519 rearrangements, by rapid evolution of **dosage compensation** or by **sexually antagonistic** mutation
520 accumulation .

521 -These hypotheses make different predictions, for example on sexual dimorphism, ploidy, **mutation**
522 **load**, **dosage compensation**, mating system or chromosomal rearrangements rates.

523

524 **Outstanding Questions Box**

525 -Is recombination suppression neutral or selected for?

526 -Are the following traits associated with progressive extensions of recombination suppression? i)
527 sexual dimorphism, ii) other types of antagonistic selection, iii) the existence of an extended diploid
528 or **dikaryotic** phase, iv) level of **mutation load** in populations (i.e., number and recessiveness of
529 deleterious mutations), v) particular mating systems (e.g., **automixis** or inbreeding), vi) number of
530 alleles at mating compatibility genes, vii) **dosage compensation** evolution, and viii) heterogamety
531 asymmetry (e.g. XY versus UV).

532 -Does progressive suppression of recombination occur in a stair-like fashion or following a more
533 continuous process?

534 -Can recombination be restored after having been suppressed? Are full reversions possible for
535 inversions? How frequently do they occur?

536 -Do overlapping inversions accumulate more rapidly than deleterious mutations following
537 recombination suppression? Does this prevent the restoration of recombination once the fitness
538 advantage of non-recombining fragments is offset by their accumulated **mutation load**?

539 -Does **dosage compensation** evolve rapidly and systematically? Are many genes sensitive to gene
540 expression levels? Can **dosage compensation** evolve in systems without sex chromosome
541 asymmetry?

542

543 **Glossary**

544 Automixis: mating between the product of a single meiosis.

545 Cis-acting factor: DNA sequence acting on the expression of a gene or on the level of
546 recombination in its local genomic environment, as opposed to *trans*-acting factors, that act on
547 distant genes or genomic regions.

548 Dikaryotic: condition in some fungi, with two genetically distinct, unfused nuclei in each cell, one
549 from each of the two parents. This situation is functionally similar to diploidy.

550 Dosage compensation: processes by which diploid gene expression level is restored following the
551 degeneration of an allele on the Y-like sex chromosome. This can involve a gene expression
552 increase in the X-like sex chromosome or of alleles in both chromosomes.

553 Evolutionary strata: segments in a non-recombining region with different levels of differentiation
554 between haplotypes (e.g. between sex chromosomes), resulting from a stepwise extension of
555 recombination cessation at different times.

556 Heterogametic: qualifies a sex producing two different types of gametes, distinguished by the sex
557 chromosome that is contained within. For example, in XY or XO systems the male is the
558 heterogametic sex, while in ZW or ZO systems the female is heterogametic.

559 Linkage disequilibrium: a situation in which two loci have alleles that are not randomly associated,
560 i.e. some allelic combinations are more frequent than expected under random association given
561 allelic frequencies.

562 Loaded: qualifies a DNA fragment carrying deleterious mutations, see mutation load below.

563 Mating types: phenotypes controlling mating compatibility, with only different mating types being
564 able to mate, without differences in gamete size.

565 Mutation load: reduction of individuals' fitness due to the presence of deleterious mutations
566 segregating in the population.

567 Overdominance: situation where the fitness of the heterozygote is higher than that of either
568 homozygous parents

569 **Permanently heterozygous allele**: an allele never found in the homozygous state. For example,
570 sex-determining alleles on Y or W chromosomes, mating-type alleles in fungi and some self-
571 incompatibility alleles in plants. Other alleles at the same locus can be homozygous, such as sex-
572 determining alleles on X chromosomes or some self-incompatibility alleles. At fungal mating-type
573 loci, all alleles are permanently heterozygous, so the locus itself is permanently heterozygous.

574 Sexual antagonism: opposing forces of selection at one or multiple loci which encode traits for
575 which females and males have different fitness optima.

576 Sheltering: Effect of masking recessive deleterious mutations from natural selection thanks to the
577 maintenance of a heterozygous state, e.g., by a linkage to a permanently heterozygous allele (Boxes
578 2 and 3).

579 Supergene: set of multiple genes inherited as a single locus due to recombination suppression.

580 Trans-acting gene expression regulators: DNA sequences regulating the expression of genes that are
581 located in a distant locus in the genome, as opposed to *cis*-acting factors, situated just nearby the
582 genes whose expression they regulate.

583 REFERENCES

- 584 1. Hill, W.G. and Robertson, A. (1966) The effect of linkage on limits to artificial selection.
585 *Genetics Research* 8, 269-294. 10.1017/S001667230800949X
- 586 2. Muller, H.J. (1932) Some genetic aspects of sex. *The American Naturalist* 66, 118-138
- 587 3. Bachtrog, D. (2013) Y-chromosome evolution : emerging insights into processes of Y-
588 chromosome degeneration. *Nature Reviews Genetics* 14, 113-124. 10.1038/nrg3366
- 589 4. Carpentier, F. *et al.* (2022) Tempo of degeneration across independently evolved
590 nonrecombining regions. *Molecular Biology and Evolution* 39, msac060.
591 10.1093/molbev/msac060
- 592 5. Marais, G.A.B. *et al.* (2018) Sex gap in aging and longevity: can sex chromosomes play a
593 role? *Biology of Sex Differences* 9, 33. 10.1186/s13293-018-0181-y
- 594 6. Teoli, J. *et al.* (2023) Transposable element expression with variation in sex chromosome
595 number supports a toxic Y effect on human longevity. *BioRxiv*
596 <https://doi.org/10.1101/2023.08.03.550779>
- 597 7. Ma, W.-J. and Rovatsos, M. (2022) Sex chromosome evolution: The remarkable diversity in
598 the evolutionary rates and mechanisms. *Journal of Evolutionary Biology* 35, 1581-1588.
599 <https://doi.org/10.1111/jeb.14119>
- 600 8. Zhou, Q. *et al.* (2014) Complex evolutionary trajectories of sex chromosomes across bird
601 taxa. *Science* 346, 1246338. 10.1126/science.1246338
- 602 9. Schield, D.R. *et al.* (2019) The origins and evolution of chromosomes, dosage
603 compensation, and mechanisms underlying venom regulation in snakes. *Genome Research*
604 29, 590-601
- 605 10. Bergero, R. *et al.* (2007) Evolutionary strata on the X chromosomes of the dioecious plant
606 *Silene latifolia*: evidence from new sex-linked genes. *Genetics* 175, 1945-1954.
607 10.1534/genetics.106.070110
- 608 11. Xu, X. *et al.* (2023) Chromosome-level genome assembly defines female-biased genes
609 associated with sex determination and differentiation in the human blood fluke *Schistosoma*
610 *japonicum*. *Molecular Ecology Resources* 23, 205-221. [https://doi.org/10.1111/1755-](https://doi.org/10.1111/1755-0998.13689)
611 0998.13689
- 612 12. Almeida, P. *et al.* (2020) Genome assembly of the basket willow, *Salix viminalis*, reveals
613 earliest stages of sex chromosome expansion. *BMC Biology* 18, 78. 10.1186/s12915-020-
614 00808-1
- 615 13. Sigeman, H. *et al.* (2019) Repeated sex chromosome evolution in vertebrates supported by
616 expanded avian sex chromosomes. *Proceedings of the Royal Society B: Biological Sciences*
617 286, 20192051. 10.1098/rspb.2019.2051
- 618 14. Wang, Z. *et al.* (2022) Phylogeny and sex chromosome evolution of Palaeognathae. *Journal*
619 *of Genetics and Genomics* 49, 109-119. <https://doi.org/10.1016/j.jgg.2021.06.013>
- 620 15. Vicoso, B. *et al.* (2013) Comparative sex chromosome genomics in snakes: differentiation,
621 evolutionary strata, and lack of global dosage compensation. *PLOS Biology* 11, e1001643.
622 10.1371/journal.pbio.1001643
- 623 16. McDaniel, S.F. *et al.* (2013) Recent gene capture on the UV sex chromosomes of the modd
624 *Ceratodon purpureus*. *Evolution* 67, 2811-2822. 10.1111/evo.12165

- 625 17. Coelho, S.M. *et al.* (2018) UV chromosomes and haploid sexual systems. *Trends in Plant*
626 *Science* 23, 794-807. 10.1016/j.tplants.2018.06.005
- 627 18. Charlesworth, D. (2023) Why and how do Y chromosome stop recombining? *Journal of*
628 *Evolutionary Biology* 36, 632-636. <https://doi.org/10.1111/jeb.14137>
- 629 19. Wright, A.E. *et al.* (2016) How to make a sex chromosome. *Nature Communications* 7,
630 12087. 10.1038/ncomms12087
- 631 20. Fisher, R. (1931) The evolution of dominance. *Biol Rev* 6, 345-368
- 632 21. Charlesworth, D. (2021) The puzzling guppy Y chromosome. *Nature Reviews Genetics* 22,
633 480-481. 10.1038/s41576-021-00369-1
- 634 22. Bergero, R. and Charlesworth, D. (2009) The evolution of restricted recombination in sex
635 chromosomes. *Trends Ecol. Evol.* 24, 94-102
- 636 23. Marais, G. and Galtier, N. (2003) Sex chromosomes: how X-Y recombination stops.
637 *Current biology : CB* 13, R641-643. 10.1016/s0960-9822(03)00570-0
- 638 24. Ironside, J.E. (2010) No amicable divorce? Challenging the notion that sexual antagonism
639 drives sex chromosome evolution. *Bioessays* 32, 718-726. 10.1002/bies.200900124
- 640 25. Ponnikas, S. *et al.* (2018) Why do sex chromosomes stop recombining? *Trends in Genetics*
641 34, 492-503. 10.1016/j.tig.2018.04.001
- 642 26. Perrin, N. (2021) Sex-chromosome evolution in frogs: what role for sex-antagonistic genes?
643 *Philosophical Transactions of the Royal Society B: Biological Sciences* 376, 20200094.
644 10.1098/rstb.2020.0094
- 645 27. Veltsos, P. *et al.* (2020) No evidence that Y-chromosome differentiation affects male fitness
646 in a Swiss population of common frogs. *Journal of Evolutionary Biology* 33, 401-409.
647 <https://doi.org/10.1111/jeb.13573>
- 648 28. Paris, J.R. *et al.* (2022) A large and diverse autosomal haplotype is associated with sex-
649 linked colour polymorphism in the guppy. *Nature Communications* 13, 1233.
650 10.1038/s41467-022-28895-4
- 651 29. Smith, S.H. *et al.* (2023) Evaluating the role of sexual antagonism in the evolution of sex
652 chromosomes: new data from fish. *Current Opinion in Genetics & Development* 81, 102078.
653 <https://doi.org/10.1016/j.gde.2023.102078>
- 654 30. Yan, Z. *et al.* (2020) Evolution of a supergene that regulates a trans-species social
655 polymorphism. *Nature Ecology & Evolution* 4, 240-249. 10.1038/s41559-019-1081-1
- 656 31. Jay, P. *et al.* (2021) Mutation load at a mimicry supergene sheds new light on the evolution
657 of inversion polymorphisms. *Nature Genetics* 53, 288-293. 10.1038/s41588-020-00771-1
- 658 32. Hartmann, F.E. *et al.* (2021) Recombination suppression and evolutionary strata around
659 mating-type loci in fungi: documenting patterns and understanding evolutionary and
660 mechanistic causes. *New Phytologist* 229, 2470-2491. 10.1111/nph.17039
- 661 33. Branco, S. *et al.* (2017) Evolutionary strata on young mating-type chromosomes despite the
662 lack of sexual antagonism. *Proceedings of the National Academy of Sciences* 114, 7067-
663 7072. 10.1073/pnas.1701658114
- 664 34. Bazzicalupo, A.L. *et al.* (2019) Little evidence of antagonistic selection in the evolutionary
665 strata of fungal mating-type chromosomes (*Microbotryum lychnidis-dioicae*). *G3-Genes*
666 *Genomes Genetics* 9, 1987-1998. 10.1534/g3.119.400242
- 667 35. Ma, W.-J. and Veltsos, P. (2021) The diversity and evolution of sex chromosomes in frogs.
668 *Genes* 12, 483. 10.3390/genes12040483
- 669 36. Filatov, D.A. (2015) Homomorphic plant sex chromosomes are coming of age. *Molecular*
670 *Ecology* 24, 3217-3219. 10.1111/mec.13268
- 671 37. Suarez-Villota, E.Y. *et al.* (2014) Homomorphic sex chromosomes and the intriguing Y
672 chromosome of *Ctenomys* rodent species (Rodentia, Ctenomyidae). *Cytogenetic and*
673 *Genome Research* 143, 232-240. 10.1159/000366173
- 674 38. Stöck, M. *et al.* (2011) Ever-young sex chromosomes in European tree frogs. *PLOS Biology*
675 9, e1001062. 10.1371/journal.pbio.1001062

- 676 39. Jay, P. *et al.* (2022) Sheltering of deleterious mutations explains the stepwise extension of
677 recombination suppression on sex chromosomes and other supergenes. *PLOS Biology* 20,
678 e3001698. 10.1371/journal.pbio.3001698
- 679 40. Lenormand, T. and Roze, D. (2022) Y recombination arrest and degeneration in the absence
680 of sexual dimorphism. *Science* 375, 663-666
- 681 41. Jeffries, D.L. *et al.* (2021) A neutral model for the loss of recombination on sex
682 chromosomes. *Philosophical Transactions of the Royal Society B: Biological Sciences* 376,
683 20200096. 10.1098/rstb.2020.0096
- 684 42. Olito, C. and Abbott, J.K. (2023) The evolution of suppressed recombination between sex
685 chromosomes and the lengths of evolutionary strata. *Evolution* 77, 1077-1090.
686 10.1093/evolut/qpaa023
- 687 43. Olito, C. *et al.* (2022) Consequences of partially recessive deleterious genetic variation for
688 the evolution of inversions suppressing recombination between sex chromosomes. *Evolution*
689 76, 1320-1330. <https://doi.org/10.1111/evo.14496>
- 690 44. Úbeda, F. *et al.* (2015) On the origin of sex chromosomes from meiotic drive. *Proceedings*
691 *of the Royal Society B: Biological Sciences* 282, 20141932. 10.1098/rspb.2014.1932
- 692 45. Charlesworth, B. (1991) The evolution of sex chromosomes. *Science* 251, 1030-1033.
693 10.1126/science.1998119
- 694 46. Charlesworth, B. and Charlesworth, D. (1978) A model for the evolution of dioecy and
695 gynodioecy. *The American Naturalist* 112, 975-997. 10.1017/CBO9781107415324.004
- 696 47. Kues, U. *et al.* (1994) A chimeric homeodomain protein causes self-incompatibility and
697 constitutive sexual development in the mushroom *Coprinus cinereus*. *Embo Journal* 13,
698 4054-4059. 10.1002/j.1460-2075.1994.tb06722.x
- 699 48. John, A. *et al.* (2016) Achiasmy: male fruit flies are not ready to mix. *Frontiers in cell and*
700 *developmental biology* 4, 75. 10.3389/fcell.2016.00075
- 701 49. Filatov, D.A. (2024) Evolution of a plant sex chromosome driven by expanding
702 pericentromeric recombination suppression. *Scientific Reports* 14, 1373. 10.1038/s41598-
703 024-51153-0
- 704 50. Bergero, R. *et al.* (2019) Exaggerated heterochiasmy in a fish with sex-linked male
705 coloration polymorphisms. *Proceedings of the National Academy of Sciences* 116, 6924-
706 6931. 10.1073/pnas.1818486116
- 707 51. Rifkin, J.L. *et al.* (2021) Widespread recombination suppression facilitates plant sex
708 chromosome evolution. *Molecular Biology and Evolution* 38, 1018-1030.
709 10.1093/molbev/msaa271
- 710 52. Rifkin, J.L. *et al.* (2022) Recombination landscape dimorphism and sex chromosome
711 evolution in the dioecious plant *Rumex hastatulus*. *Philosophical Transactions of the Royal*
712 *Society B: Biological Sciences* 377, 20210226. 10.1098/rstb.2021.0226
- 713 53. Vittorelli, N. *et al.* (2023) Stepwise recombination suppression around the mating-type locus
714 in an ascomycete fungus with self-fertile spores. *PLOS Genetics* 19, e1010347.
715 10.1371/journal.pgen.1010347
- 716 54. Villtoureix, R. *et al.* (2023) Inversion breakpoints and the evolution of supergenes.
717 *Molecular Ecology* 30, 2738-2755
- 718 55. Kirkpatrick, M. (2010) How and why chromosome inversions evolve. *PLoS Biology* 8,
719 e1000501. 10.1371/journal.pbio.1000501
- 720 56. Dobzhansky, T. (1970) Genetics of the Evolutionary Process. In, Columbia University Press
- 721 57. Charlesworth, D. *et al.* (2005) Steps in the evolution of heteromorphic sex chromosomes.
722 *Heredity* 95, 118-128. 10.1038/sj.hdy.6800697
- 723 58. Rice, W.R. (1984) Sex chromosomes and the evolution of sexual dimorphism. *Evolution*
724 *International Journal of Organic Evolution* 38, 735-742
- 725 59. Cavoto, E. *et al.* (2018) Sex-antagonistic genes, XY recombination and feminized Y
726 chromosomes. *Journal of Evolutionary Biology* 31, 416-427.
727 <https://doi.org/10.1111/jeb.13235>

- 728 60. Kirkpatrick, M. and Barton, N. (2006) Chromosome inversions, local adaptation and
729 speciation. *Genetics* 173, 419-434. 10.1534/genetics.105.047985
- 730 61. Lasne, C. *et al.* (2017) The relative contributions of the X chromosome and autosomes to
731 local adaptation. *Genetics* 205, 1285-1304. 10.1534/genetics.116.194670
- 732 62. Nei, M. *et al.* (1967) Frequency changes of new inversions in populations under mutation-
733 selection equilibria *Genetics* 57, 741-750. 10.1093/genetics/57.4.741
- 734 63. Rasmuson, M. (1980) Linkage to a self-sterility locus. Consequences for segregation and
735 selection. *Hereditas* 92, 315-319
- 736 64. Antonovics, J. and Abrams, J.Y. (2004) Intratetrad mating and the evolution of linkage
737 relationships. *Evolution* 58, 702-709
- 738 65. Zakharov, I.A. (2023) Intratetrad mating as the driving force behind the formation of sex
739 chromosomes in fungi. *Trends in Genetics and Evolution* 6,
740 10.24294/tge.v24296i24291.22522
- 741 66. Charlesworth, B. *et al.* (1987) The relative rates of evolution of sex-chromosomes and
742 autosomes. *Am Nat* 130, 113-146
- 743 67. Charlesworth, D. (2017) Evolution of recombination rates between sex chromosomes.
744 *Philosophical Transactions of the Royal Society B: Biological Sciences* 372, 20160456.
745 10.1098/rstb.2016.0456
- 746 68. Kent, T.V. *et al.* (2017) Coevolution between transposable elements and recombination.
747 *Philosophical Transactions of the Royal Society B-Biological Sciences* 372, 20160458.
748 10.1098/rstb.2016.0458
- 749 69. Lande, R. (1985) The fixation of chromosomal rearrangements in a subdivided population
750 with local extinction and colonization. *Heredity* 54, 323-332. 10.1038/hdy.1985.43
- 751 70. Boideau, F. *et al.* (2022) Epigenomic and structural events preclude recombination in
752 *Brassica napus*. *New Phytologist* 234, 545-559. <https://doi.org/10.1111/nph.18004>
- 753 71. Mirouze, M. *et al.* (2012) Loss of DNA methylation affects the recombination landscape in
754 *Arabidopsis*. *Proceedings of the National Academy of Sciences* 109, 5880-5885.
755 10.1073/pnas.1120841109
- 756 72. Li, S.F. *et al.* (2016) Repetitive sequences and epigenetic modification: inseparable partners
757 play important roles in the evolution of plant sex chromosomes. *Planta* 243, 1083-1095.
758 10.1007/s00425-016-2485-7
- 759 73. Connallon, T. and Olito, C. (2022) Natural selection and the distribution of chromosomal
760 inversion lengths. *Molecular Ecology* 31, 3627-3641. <https://doi.org/10.1111/mec.16091>
- 761 74. Wang, J. *et al.* (2013) A Y-like social chromosome causes alternative colony organization in
762 fire ants. *Nature* 493, 664. 10.1038/nature11832
- 763 75. Olito, C. and Charlesworth, B. (2023) Do deleterious mutations promote the evolution of
764 recombination suppression between X and Y chromosomes? *BioRxiv*
765 <https://www.biorxiv.org/content/10.1101/2023.11.27.568803v1>,
- 766 76. Berdan, E.L. *et al.* (2021) Deleterious mutation accumulation and the long-term fate of
767 chromosomal inversions. *PLOS Genetics* 17, e1009411. 10.1371/journal.pgen.1009411
- 768 77. Nei, M. (1970) Accumulation of nonfunctional genes on sheltered chromosomes. *Am Nat.*
769 104, 311-322
- 770 78. Badouin, H. *et al.* (2015) Chaos of rearrangements in the mating-type chromosomes of the
771 anther-smut fungus *Microbotryum lychnidis-dioicae*. *Genetics* 200, 1275-1284.
772 10.1534/genetics.115.177709
- 773 79. Branco, S. *et al.* (2018) Multiple convergent supergene evolution events in mating-type
774 chromosomes. *Nature Communications* 9, 2000. 10.1038/s41467-018-04380-9
- 775 80. Sun, Y. *et al.* (2017) Large-scale suppression of recombination predates genomic
776 rearrangements in *Neurospora tetrasperma*. *Nature Communications* 8, 1140.
777 10.1038/s41467-017-01317-6
- 778 81. Zhou, Y. *et al.* (2023) Eighty million years of rapid evolution of the primate Y chromosome.
779 *Nature Ecology & Evolution* 7, 1114-1130. 10.1038/s41559-022-01974-x

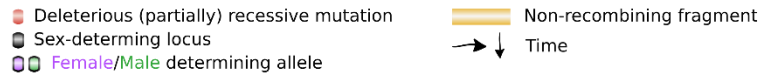
- 780 82. Hallast, P. *et al.* (2023) Assembly of 43 human Y chromosomes reveals extensive
781 complexity and variation. *Nature* 621, 355-364. 10.1038/s41586-023-06425-6
- 782 83. Peichel, C.L. *et al.* (2020) Assembly of the threespine stickleback Y chromosome reveals
783 convergent signatures of sex chromosome evolution. *Genome Biology* 21, 177.
784 10.1186/s13059-020-02097-x
- 785 84. Jeffries, D.L. *et al.* (2018) A rapid rate of sex-chromosome turnover and non-random
786 transitions in true frogs. *Nature Communications* 9, 4088. 10.1038/s41467-018-06517-2
- 787 85. Lenormand, T. *et al.* (2020) Sex chromosome degeneration by regulatory evolution. *Current*
788 *Biology* 30, 3001-3006.e3005. 10.1016/j.cub.2020.05.052
- 789 86. Lenormand, T. and Roze, D. (2024) Can mechanistic constraints on recombination
790 reestablishment explain the long-term maintenance of degenerate sex chromosomes?? *Peer*
791 *Community Journal* 4, e17
- 792 87. Ruzicka, F. and Connallon, T. (2022) An unbiased test reveals no enrichment of sexually
793 antagonistic polymorphisms on the human X chromosome. *Proceedings of the Royal Society*
794 *B: Biological Sciences* 289, 20212314. 10.1098/rspb.2021.2314
- 795 88. Innocenti, P. and Morrow, E.H. (2010) The sexually antagonistic genes of *Drosophila*
796 *melanogaster*. *PLoS Biology* 8, e1000335. 10.1371/journal.pbio.1000335
- 797 89. Huylmans, A.K. *et al.* (2019) Sex-biased gene expression and dosage compensation on the
798 *Artemia franciscana* Z-Chromosome. *Genome Biology and Evolution* 11, 1033-1044.
799 10.1093/gbe/evz053
- 800 90. Ruzicka, F. *et al.* (2019) Genome-wide sexually antagonistic variants reveal long-standing
801 constraints on sexual dimorphism in fruit flies. *PLoS Biology* 17, e3000244.
802 10.1371/journal.pbio.3000244
- 803 91. Winge, O. (1927) The location of eighteen genes in *Lebistes reticulata*. *J. Genet.* 18, 1-43
- 804 92. Wright, A.E. *et al.* (2017) Convergent recombination suppression suggests role of sexual
805 selection in guppy sex chromosome formation. *Nature Communications* 8, 14251.
806 10.1038/ncomms14251
- 807 93. Wright, A.E. *et al.* (2019) On the power to detect rare recombination events. *Proceedings of*
808 *the National Academy of Sciences* 116, 12607-12608. 10.1073/pnas.1905555116
- 809 94. Shearn, R. *et al.* (2020) Evolutionary stasis of the pseudoautosomal boundary in
810 strepsirrhine primates. *eLife* 9, e63650. 10.7554/eLife.63650
- 811 95. Duhamel, M. *et al.* (2022) Onset and stepwise extensions of recombination suppression are
812 common in mating-type chromosomes of *Microbotryum* anther-smut fungi. *J Evol Biol* 35,
813 1619-1634
- 814 96. Hartmann, F.E. *et al.* (2021) Size variation of the nonrecombining region on the mating-type
815 chromosomes in the fungal *Podospira anserina* species complex. *Molecular Biology and*
816 *Evolution* 38, 2475-2492. 10.1093/molbev/msab040
- 817 97. Charlesworth, B. and Wall, J.D. (1999) Inbreeding, heterozygote advantage and the
818 evolution of neo-X and neo-Y sex chromosomes. *Proceedings of the Royal Society B-*
819 *Biological Sciences* 266, 51-56
- 820 98. Fontana, F. (1991) Multiple reciprocal chromosomal translocations and their role in the
821 evolution of sociality in termites. *Ethology Ecology & Evolution* 3, 15-19.
822 10.1080/03949370.1991.10721901
- 823 99. Luykx, P. (1990) A cytogenetic survey of 25 species of lower termites from Australia.
824 *Genome* 33, 80-88. 10.1139/g90-013
- 825 100. Foulongne-Oriol, M. *et al.* (2021) Mating-type locus organization and mating-type
826 chromosome differentiation in the bipolar edible button mushroom *Agaricus bisporus*.
827 *Genes*. 10.3390/genes12071079
- 828 101. Menkis, A. *et al.* (2008) The mating-type chromosome in the filamentous ascomycete
829 *Neurospora tetrasperma* represents a model for early evolution of sex chromosomes. *PLoS*
830 *Genet.* 4, e1000030

- 831 102. Grognet, P. *et al.* (2014) Maintaining two mating types: structure of the mating type locus
832 and its role in heterokaryosis in *Podospora anserina*. *Genetics* 197, 421-432.
833 10.1534/genetics.113.159988
- 834 103. Goubet, P.M. *et al.* (2012) Contrasted patterns of molecular evolution in dominant and
835 recessive self-incompatibility haplotypes in *Arabidopsis*. *PLOS Genetics* 8, e1002495.
836 10.1371/journal.pgen.1002495
- 837 104. Immler, S. and Otto, S.P. (2018) The evolutionary consequences of selection at the haploid
838 gametic stage. *Am Nat* 192, 241-249. 10.1086/698483
- 839 105. Immler, S. and Otto, S.P. (2015) The evolution of sex chromosomes in organisms with
840 separate haploid sexes. *Evolution* 69, 694-708. 10.1111/evo.12602
- 841 106. Malkus, A. *et al.* (2009) Genetic linkage map of *Phaeosphaeria nodorum*, the causal agent
842 of stagonospora nodorum blotch disease of wheat. *European Journal of Plant Pathology*
843 124, 681-690. 10.1007/s10658-009-9454-y
- 844 107. Ellwood, S.R. *et al.* (2010) A first genome assembly of the barley fungal pathogen
845 *Pyrenophora teres f. teres*. *Genome Biology* 11, R109. 10.1186/gb-2010-11-11-r109
- 846 108. Heesch, S. *et al.* (2021) Evolution of life cycles and reproductive traits: Insights from the
847 brown algae. *Journal of Evolutionary Biology* 34, 992-1009.
848 <https://doi.org/10.1111/jeb.13880>
- 849 109. Coelho, S.M. *et al.* (2019) Origin and evolution of sex-determination systems in the brown
850 algae. *New Phytologist* 222, 1751-1756. <https://doi.org/10.1111/nph.15694>
- 851 110. Ahmed, S. *et al.* (2014) A haploid system of sex determination in the brown alga
852 *Ectocarpus* sp. *Current Biology* 24, 1945-1957. 10.1016/j.cub.2014.07.042
- 853 111. De Hoff, P.L. *et al.* (2013) Species and population level molecular profiling reveals cryptic
854 recombination and emergent asymmetry in the dimorphic mating locus of *C. reinhardtii*.
855 *PLOS Genetics* 9, e1003724. 10.1371/journal.pgen.1003724
- 856 112. Iwasaki, M. *et al.* (2021) Identification of the sex-determining factor in the liverwort
857 *Marchantia polymorpha* reveals unique evolution of sex chromosomes in a haploid system.
858 *Current Biology* 31, 5522-5532.e5527. <https://doi.org/10.1016/j.cub.2021.10.023>
- 859 113. Ferris, P. *et al.* (2010) Evolution of an expanded sex-determining locus in *Volvox*. *Science*
860 328, 351-354. 10.1126/science.1186222
- 861 114. Hartl, D.L. and Clark, A.G. (2006) *Principles of Population Genetics 4th Edition* Sinauer
862 Associates, Oxford University Press
- 863 115. Benegas, G. *et al.* (2023) DNA language models are powerful predictors of genome-wide
864 variant effects. 120, e2311219120. 10.1073/pnas.2311219120
- 865 116. Bergeron, L.A. *et al.* (2023) Evolution of the germline mutation rate across vertebrates.
866 *Nature* 615, 285-291
- 867 117. Pei, Y. *et al.* (2023) Weak antagonistic fitness effects can maintain an inversion
868 polymorphism. *Molecular Ecology* n/a. <https://doi.org/10.1111/mec.16963>
- 869 118. Knief, U. *et al.* (2017) A sex-chromosome inversion causes strong overdominance for sperm
870 traits that affect siring success. *Nat Ecol Evol* 1, 1177-1184. 10.1038/s41559-017-0236-1
- 871 119. Lahn, B.T. and Page, D.C. (1999) Four evolutionary strata on the human X chromosome.
872 *Science (New York, N.Y.)* 286, 964-967. 10.1126/science.286.5441.964
- 873 120. Skaletsky, H. *et al.* (2003) The male-specific region of the human Y chromosome is a
874 mosaic of discrete sequence classes. *Nature* 423, 825-837. 10.1038/nature01722
- 875 121. Bellott, D.W. *et al.* (2014) Mammalian Y chromosomes retain widely expressed dosage-
876 sensitive regulators. *Nature* 508, 494-499. 10.1038/nature13206
- 877 122. Nam, K. and Ellegren, H. (2008) The chicken (*Gallus gallus*) Z chromosome contains at
878 least three nonlinear evolutionary strata. *Genetics* 180, 1131-1136.
879 10.1534/genetics.108.090324
- 880 123. Wang, J. *et al.* (2012) Sequencing papaya X and Yh chromosomes reveals molecular basis
881 of incipient sex chromosome evolution. *Proceedings of the National Academy of Sciences*
882 109, 13710-13715. 10.1073/pnas.1207833109

- 883 124. Roesti, M. *et al.* (2013) Recombination in the threespine stickleback genome—patterns and
884 consequences. *Molecular Ecology* 22, 3014-3027. <https://doi.org/10.1111/mec.12322>
- 885 125. Natri, H.M. *et al.* (2013) Progressive recombination suppression and differentiation in
886 recently evolved neo-sex chromosomes. *Molecular Biology and Evolution* 30, 1131-1144.
887 10.1093/molbev/mst035
- 888 126. Van Laere, A.S. *et al.* (2008) Characterization of the bovine pseudoautosomal boundary:
889 Documenting the evolutionary history of mammalian sex chromosomes. *Genome Res* 18,
890 1884-1895. 10.1101/gr.082487.108
- 891 127. White, M.A. *et al.* (2012) A pronounced evolutionary shift of the pseudoautosomal region
892 boundary in house mice. *Mammalian Genome* 23, 454-466. 10.1007/s00335-012-9403-5
- 893 128. Furman, B.L.S. *et al.* (2020) Sex chromosome evolution: so many exceptions to the rules.
894 *Genome Biology and Evolution* 12, 750-763. 10.1093/gbe/evaa081
- 895 129. Moraga, C. and al., E. (2023) The *Silene latifolia* genome and its giant Y chromosome.
896 *BioRxiv* <https://www.biorxiv.org/content/10.1101/2023.09.21.558754v1>,
- 897 130. Lucotte, E. *et al.* (2024) Repeated loss of function at HD mating-type genes and of
898 recombination suppression without mating-type locus linkage in anther-smut fungi. *BioRxiv*
899 <https://www.biorxiv.org/content/10.1101/2024.03.03.583181v1>,
- 900 131. Duhamel, M. *et al.* (2023) Dynamics of transposable element accumulation in the non-
901 recombining regions of mating-type chromosomes in anther-smut fungi. *Nature*
902 *Communications* in press. 10.1101/2022.08.03.502670
- 903 132. Sacchi, B.M. *et al.* (2023) Phased assembly of neo-sex chromosomes reveals extensive Y
904 degeneration and rapid genome evolution in *Rumex hastatulus*. *BioRxiv*
905 <https://www.biorxiv.org/content/10.1101/2023.09.26.559509v1.full.pdf>,
- 906 133. Krimbas, C.B. and Powell, J.R. (1992) Introduction. In *Drosophila Inversion*
907 *Polymorphism* (Krimbas, C.B. and Powell, J.R., eds), pp. 1-52, CRC Press
- 908 134. Porubsky, D. *et al.* (2021) Haplotype-resolved inversion landscape reveals hotspots of
909 mutational recurrence associated with genomic disorders. *BioRxiv*
910 <https://doi.org/10.1101/2021.12.20.472354>,
- 911 135. Blaser, O. *et al.* (2014) Sex-chromosome turnovers: the hot-potato model. *The American*
912 *Naturalist* 183, 140-146
- 913 136. Connallon, T. *et al.* (2018) Local adaptation and the evolution of inversions on sex
914 chromosomes and autosomes. *Philosophical Transactions of the Royal Society B: Biological*
915 *Sciences* 373, 20170423. 10.1098/rstb.2017.0423
- 916 137. Belyeu, J.R. *et al.* (2021) De novo structural mutation rates and gamete-of-origin biases
917 revealed through genome sequencing of 2,396 families. *The American Journal of Human*
918 *Genetics* 108, 597-607. <https://doi.org/10.1016/j.ajhg.2021.02.012>
- 919 138. Veltsos, P. *et al.* (2019) Early sex-chromosome evolution in the diploid dioecious plant
920 *Mercurialis annua*. *Genetics* 212, 815-835. 10.1534/genetics.119.302045
- 921 139. Wei, K.H. and Bachtrog, D. (2019) Ancestral male recombination in *Drosophila albomicans*
922 produced geographically restricted neo-Y chromosome haplotypes varying in age and onset
923 of decay. 15, e1008502. 10.1371/journal.pgen.1008502
- 924 140. Hough, J. *et al.* (2014) Genetic degeneration of old and young y chromosomes in the
925 flowering plant *Rumex hastatulus*. *Proceedings of the National Academy of Sciences of the*
926 *United States of America* 111, 7713-7718. 10.1073/pnas.1319227111
- 927 141. Liu, J. *et al.* (2021) Transcriptional regulation of dosage compensation in *Carica papaya*.
928 *Scientific Reports* 11, 5854. 10.1038/s41598-021-85480-3
- 929 142. Schultheiß, R. *et al.* (2015) Spatial dynamics of evolving dosage compensation in a young
930 sex chromosome system. *Genome Biology and Evolution* 7, 581-590. 10.1093/gbe/evv013
- 931 143. Wright, A.E. *et al.* (2012) Trade-off between selection for dosage compensation and
932 masculinization on the avian Z chromosome. *Genetics* 192, 1433-1445.
933 10.1534/genetics.112.145102

- 934 144. Graves, J.A. and Disteché, C.M. (2007) Does gene dosage really matter? *Journal of biology*
935 6, 1. 10.1186/jbiol55
- 936 145. Ellegren, H. *et al.* (2007) Faced with inequality: chicken do not have a general dosage
937 compensation of sex-linked genes. *BMC Biology* 5, 40. 10.1186/1741-7007-5-40
- 938 146. Kalita, A.I. *et al.* (2023) The sex-specific factor SOA controls dosage compensation in
939 *Anopheles* mosquitos. 10.1038/s41586-023-06641-0
- 940 147. Brockdorff, N. and Turner, B.M. (2015) Dosage compensation in mammals. *Cold Spring*
941 *Harbor perspectives in biology* 7, a019406. 10.1101/cshperspect.a019406
- 942 148. Hoffmann, A.A. and Rieseberg, L.H. (2008) Revisiting the impact of inversions in
943 evolution: from population genetic markers to drivers of adaptive shifts and speciation?
944 *Annual review of ecology, evolution, and systematics* 39, 21-42.
945 10.1146/annurev.ecolsys.39.110707.173532
- 946 149. Koury, S.A. (2023) Predicting recombination suppression outside chromosomal inversions
947 in *Drosophila melanogaster* using crossover interference theory. *Heredity* 130, 196-208.
948 10.1038/s41437-023-00593-x
- 949 150. Corbett-Detig, R.B. (2016) Selection on inversion breakpoints favors proximity to pairing
950 sensitive sites in *Drosophila melanogaster*. *Genetics* 204, 259-265.
951 10.1534/genetics.116.190389
- 952 151. Lemaitre, C. *et al.* (2009) Footprints of inversions at present and past pseudoautosomal
953 boundaries in human sex chromosomes. *Genome Biology and Evolution* 1, 56-66.
954 10.1093/gbe/evp006
- 955 152. Carpentier, F. *et al.* (2019) Convergent recombination cessation between mating-type genes
956 and centromeres in selfing anther-smut fungi. *Genome Research* 29, 944-953.
957 10.1101/gr.242578.118.5
- 958 153. Boideau, F. *et al.* (2022) Epigenomic and structural events preclude recombination in
959 *Brassica napus*. 234, 545-559. 10.1111/nph.18004
- 960 154. Gorelick, R. (2003) Evolution of dioecy and sex chromosomes via methylation driving
961 Muller's ratchet. *Biological Journal of the Linnean Society* 80, 353-368. 10.1046/j.1095-
962 8312.2003.00244.x
- 963 155. Yelina, N.E. *et al.* (2012) Epigenetic remodeling of meiotic crossover frequency in
964 *Arabidopsis thaliana* DNA methyltransferase mutants. *PLoS Genet* 8, e1002844.
965 10.1371/journal.pgen.1002844
- 966 156. Zamudio, N. *et al.* (2015) DNA methylation restrains transposons from adopting a
967 chromatin signature permissive for meiotic recombination. *Genes & development* 29, 1256-
968 1270. 10.1101/gad.257840.114
- 969 157. Maloisel, L. and Rossignol, J.L. (1998) Suppression of crossing-over by DNA methylation
970 in *Ascobolus*. *Genes & development* 12, 1381-1389. 10.1101/gad.12.9.1381
- 971 158. Baudat, F. *et al.* (2010) PRDM9 is a major determinant of meiotic recombination hotspots in
972 humans and mice. *Science* 327, 836-840. 10.1126/science.1183439
- 973 159. Singhal, S. *et al.* (2015) Stable recombination hotspots in birds. *Science* 350, 928-932.
974 10.1126/science.aad0843
- 975 160. Legrand, S. *et al.* (2024) Absence of chromosome axis protein recruitment prevents meiotic
976 recombination chromosome-wide in the budding yeast *Lachancea kluyveri*. *Proceedings of*
977 *the National Academy of Sciences* 121, e2312820121. 10.1073/pnas.2312820121
- 978 161. Greig, D. *et al.* (2003) A role for the mismatch repair system during incipient speciation in
979 *Saccharomyces*. *Journal of Evolutionary Biology* 16, 429-437.
980 <https://doi.org/10.1046/j.1420-9101.2003.00546.x>
- 981 162. Datta, A. *et al.* (1996) Mitotic crossovers between diverged sequences are regulated by
982 mismatch repair proteins in *Saccaromyces cerevisiae*. *Molecular and cellular biology* 16,
983 1085-1093. 10.1128/mcb.16.3.1085

- 984 163. Li, L. *et al.* (2006) The impact of sequence divergence and DNA mismatch repair on
985 homeologous recombination in *Arabidopsis*. *The Plant journal : for cell and molecular*
986 *biology* 45, 908-916. 10.1111/j.1365-313X.2006.02657.x
- 987 164. Fisher, R.A. (1935) The sheltering of lethals. *Am. Nat.* 69, 446-455
- 988 165. Feldman, M.W. (1972) Selection for linkage modification: I. Random mating populations.
989 *Theoretical Population Biology* 3, 324-346. [https://doi.org/10.1016/0040-5809\(72\)90007-X](https://doi.org/10.1016/0040-5809(72)90007-X)
- 990 166. Holsinger, K.E. and Feldman, M.W. (1985) Selection in complex genetic systems. VI.
991 Equilibrium properties of two locus selection models with partial selfing. *Theoretical*
992 *Population Biology* 28, 117-132. [https://doi.org/10.1016/0040-5809\(85\)90024-3](https://doi.org/10.1016/0040-5809(85)90024-3)
- 993 167. Leach, C.R. *et al.* (1986) Linkage disequilibrium and gametophytic self-incompatibility.
994 *Theor. Appl. Genet.* 73, 102-112
- 995 168. John, S. and Jain, K. (2015) Effect of drift, selection and recombination on the equilibrium
996 frequency of deleterious mutations. *Journal of Theoretical Biology* 365, 238-246.
997 10.1016/j.jtbi.2014.10.023
- 998 169. Garcia-Dorado, A. *et al.* (2007) The build up of mutation-selection-drift balance in
999 laboratory *Drosophila* populations. *Evolution* 61, 653-665. 10.1111/j.1558-
1000 5646.2007.00052.x
- 1001 170. Spigler, R.B. *et al.* (2017) Inbreeding depression and drift load in small populations at
1002 demographic disequilibrium. *Evolution* 71, 81-94. 10.1111/evo.13103
- 1003

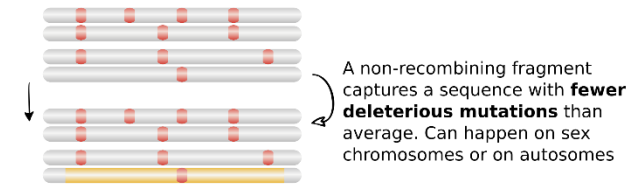


1. Initial advantage of recombination suppression

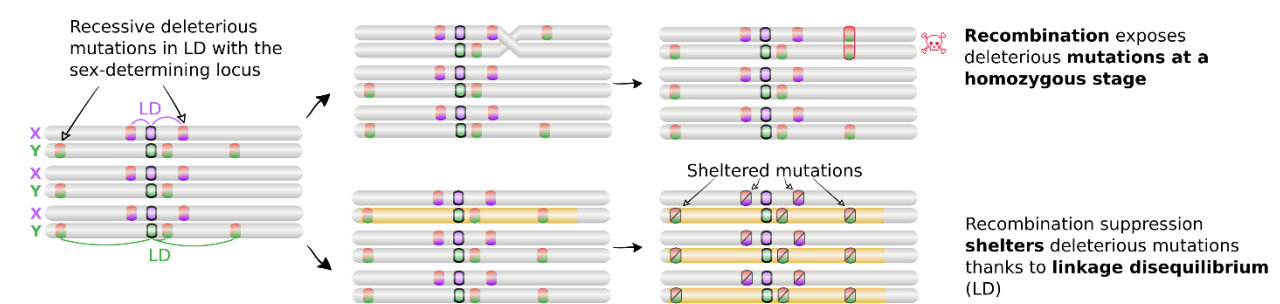
a Sexual antagonism hypothesis



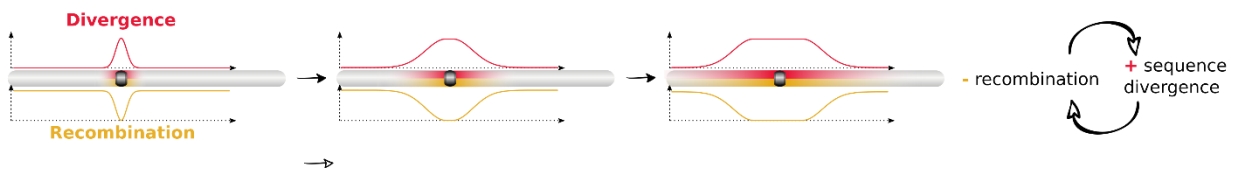
b Lower-load or lucky fragment hypothesis



c Initial-sheltering hypothesis

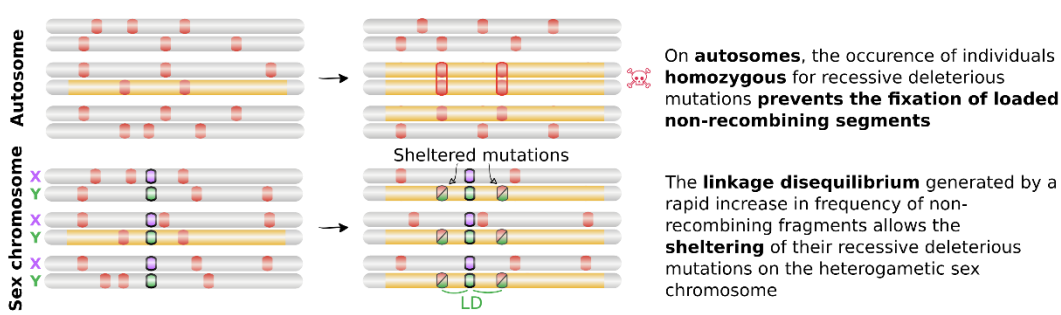


d Neutral hypothesis: divergence-recombination feedback loop



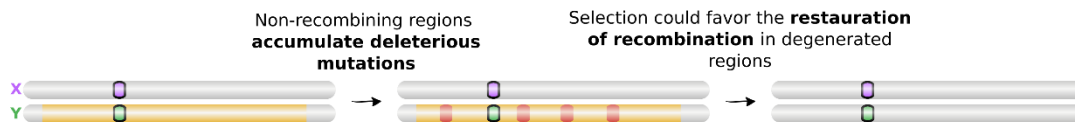
2. Fixation of non-recombining fragments: the fixation-sheltering hypothesis

e Sheltering of deleterious mutations

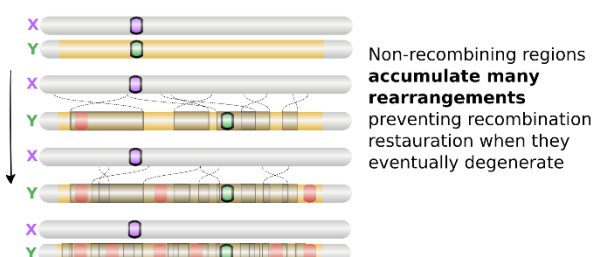


3. Long-term maintenance of recombination suppression

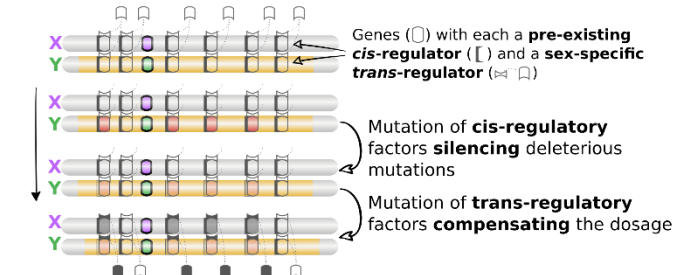
f Degeneration of non-recombining regions could favor the restoration of recombination



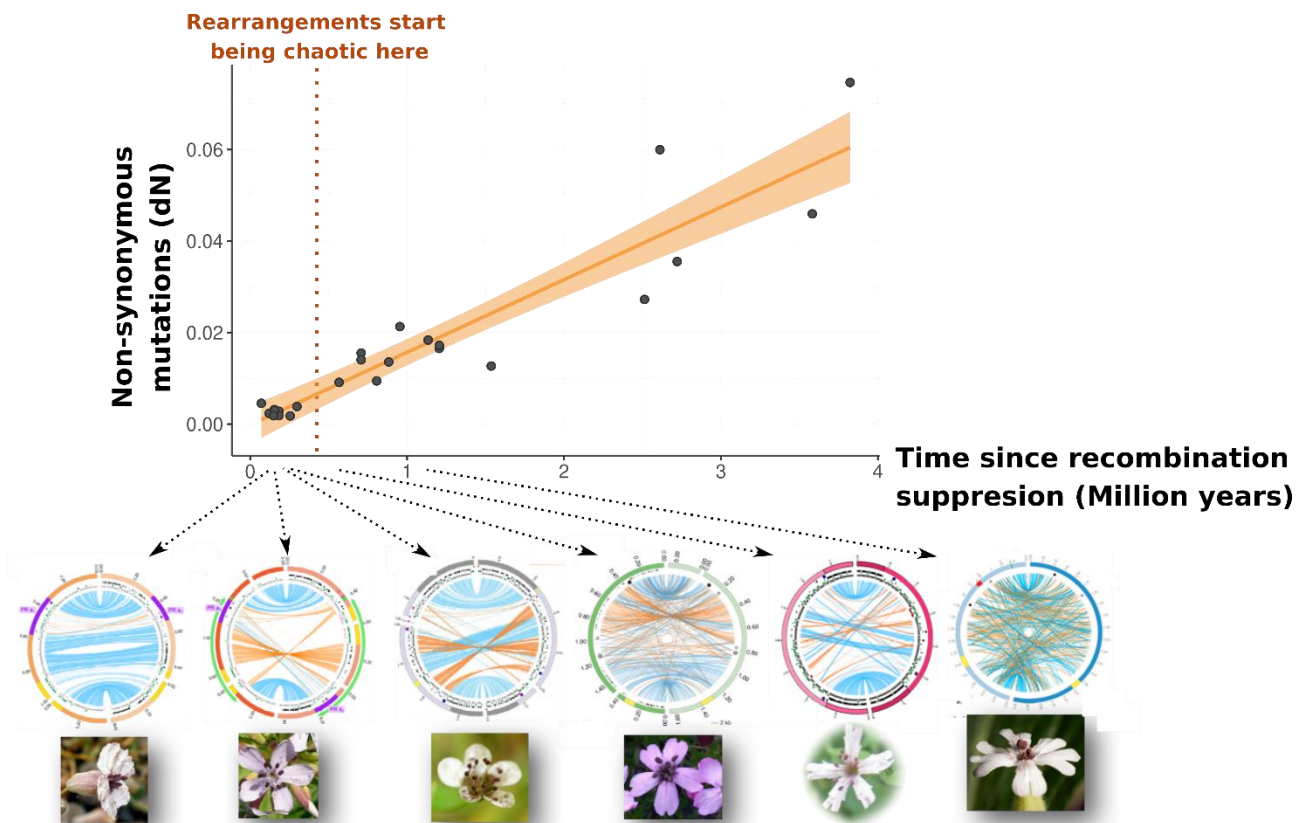
g Rearrangement-constraint hypothesis



h Regulatory hypothesis



1006 **Figure 1: Illustration of the different stages and hypotheses for explaining the progressive loss**
 1007 **of recombination on sex chromosomes and other supergenes.** The first stage depicts hypotheses
 1008 regarding the initial evolutionary mechanisms explaining the rise in frequency of non-recombining
 1009 fragments (a: **sexual antagonism**, b: lower **load** than average, c: drift, d: initial deleterious mutation
 1010 **sheltering**). The second stage deals with the fixation of non-recombining fragments despite
 1011 captured or accumulated **mutation load** thanks to **sheltering** (e). The third stage is the persistence
 1012 of non-recombining fragments on the long term despite deleterious mutation accumulation (f),
 1013 thanks to physical constraints due to multiple overlapping rearrangements (g) or due to early **dosage**
 1014 **compensation** (h).

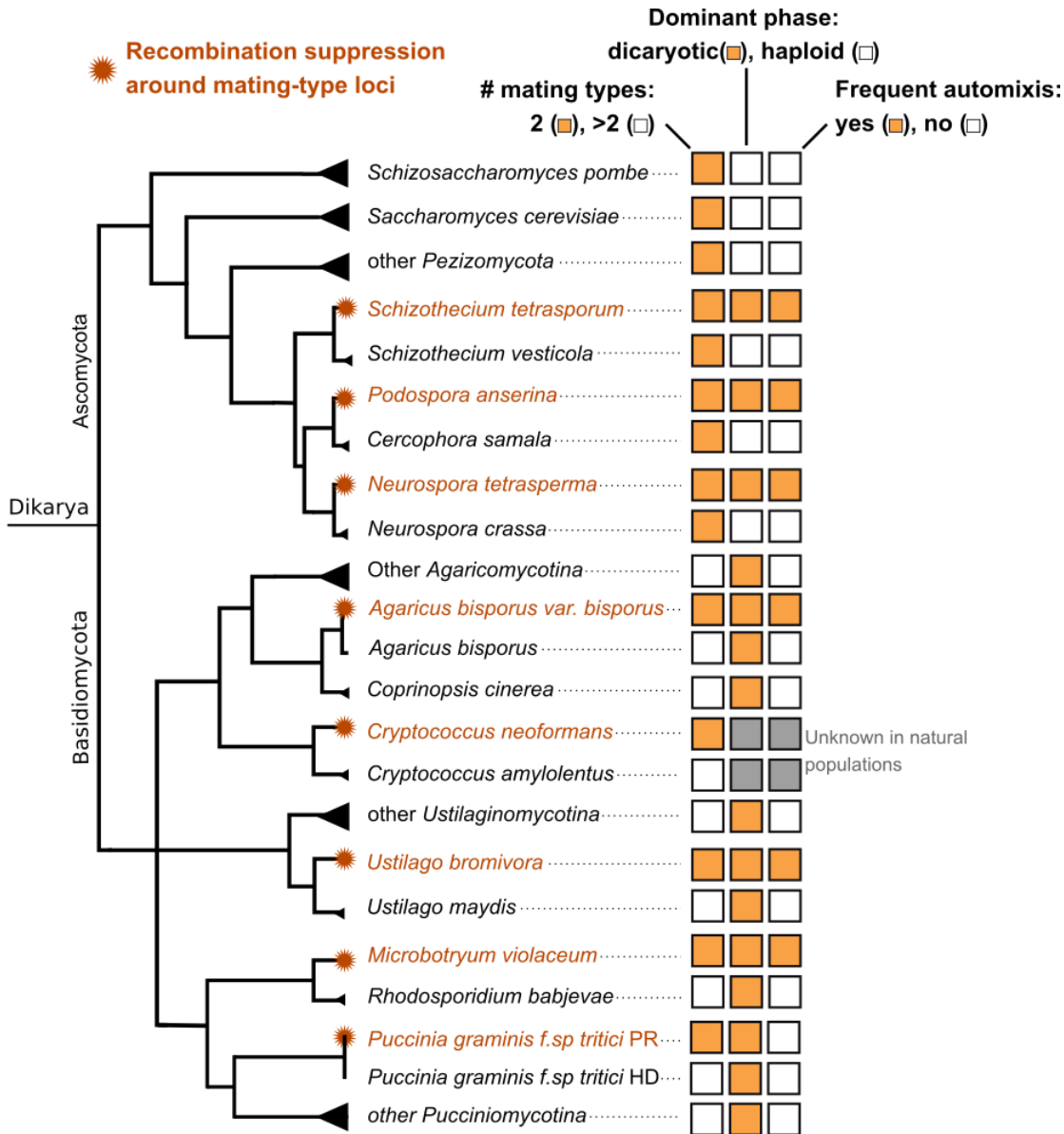


1015

1016 **Figure 2: Comparison of the accumulation dynamics of non-synonymous substitutions (as a proxy**
 1017 **for deleterious mutations) and of rearrangements, in the non-recombining regions of mating-type**
 1018 **chromosomes of various ages in anther-smut fungi; figures adapted from [4,79,95].** The points
 1019 correspond to non-synonymous substitutions between alleles on the two **mating-type** chromosomes
 1020 in 22 independent events of recombination suppression (**evolutionary strata**), in 13 *Microbotryum*
 1021 species. Circos plots display the synteny levels between the two **mating-type** chromosomes in six
 1022 *Microbotryum* species, with collinear regions in blue and inverted regions in orange.
 1023 Rearrangements are already chaotic when non-synonymous substitutions begin to accumulate.

1024 Pictures of the corresponding *Microbotryum* species are shown as spores in the anthers of their host
 1025 plants (credit: Michael E. Hood).

1026



1027

1028 **Figure 3:** Recombination suppression seems associated in fungi to the existence of a substantial
 1029 **dikaryotic** phase (in opposition to haploid fungi), with only two **mating-type** alleles, and
 1030 sometimes with an **automictic** mating system. A **dikaryotic** or diploid main phase and an
 1031 automatic mating system are indeed predicted to be associated with the evolution of stepwise
 1032 recombination suppression under hypotheses involving deleterious mutations. In addition, when
 1033 multiple alleles are present at mating incompatibility loci, there can be a turnover of alleles, with the
 1034 loss of the alleles around which recombination suppression has evolved, once they have
 1035 accumulated too many deleterious mutations.