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

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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.

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393 **Author contributions**

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396

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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](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.

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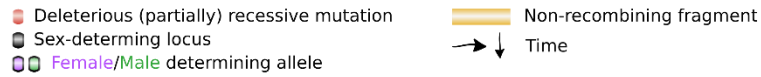
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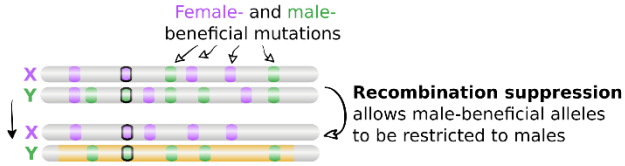
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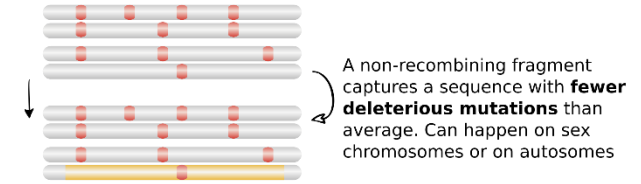


**1. Initial advantage of recombination suppression**

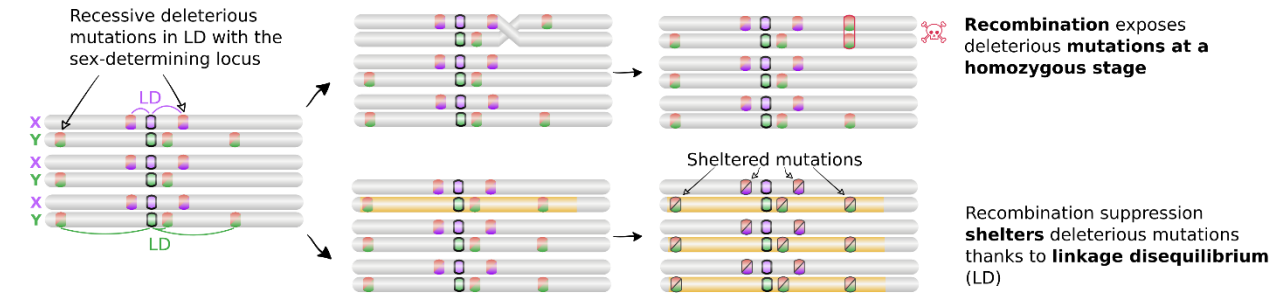
**a Sexual antagonism hypothesis**



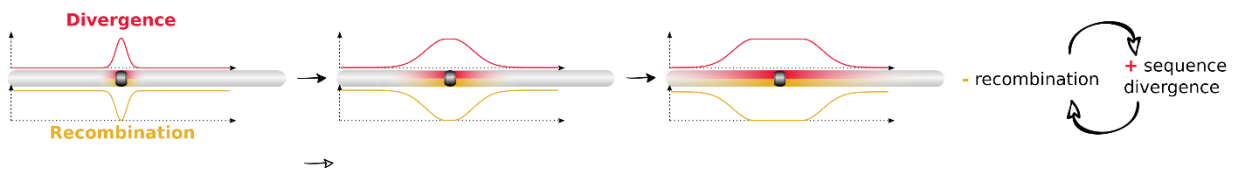
**b Lower-load or lucky fragment hypothesis**



**c Initial-sheltering hypothesis**

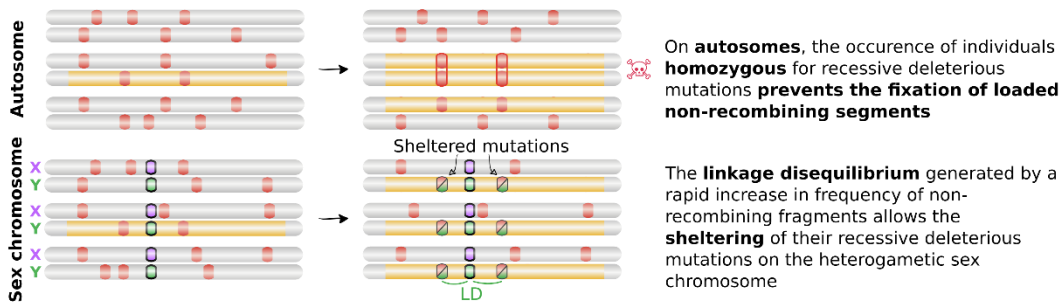


**d Neutral hypothesis: divergence-recombination feedback loop**



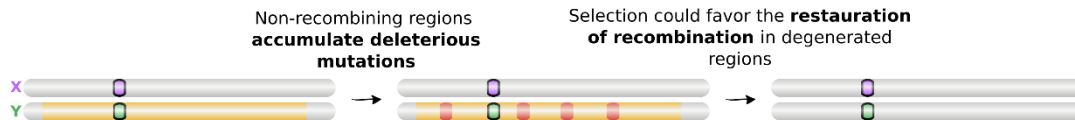
**2. Fixation of non-recombining fragments: the fixation-sheltering hypothesis**

**e Sheltering of deleterious mutations**

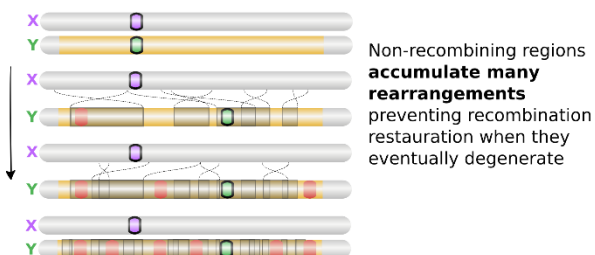


**3. Long-term maintenance of recombination suppression**

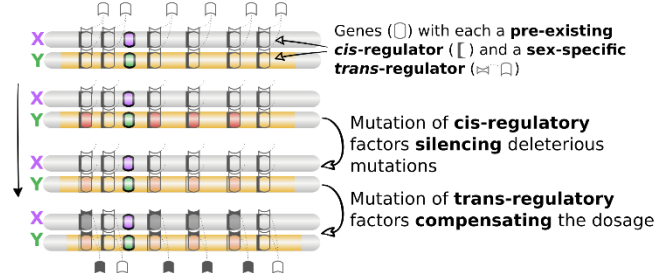
**f Degeneration of non-recombining regions could favor the restoration of recombination**



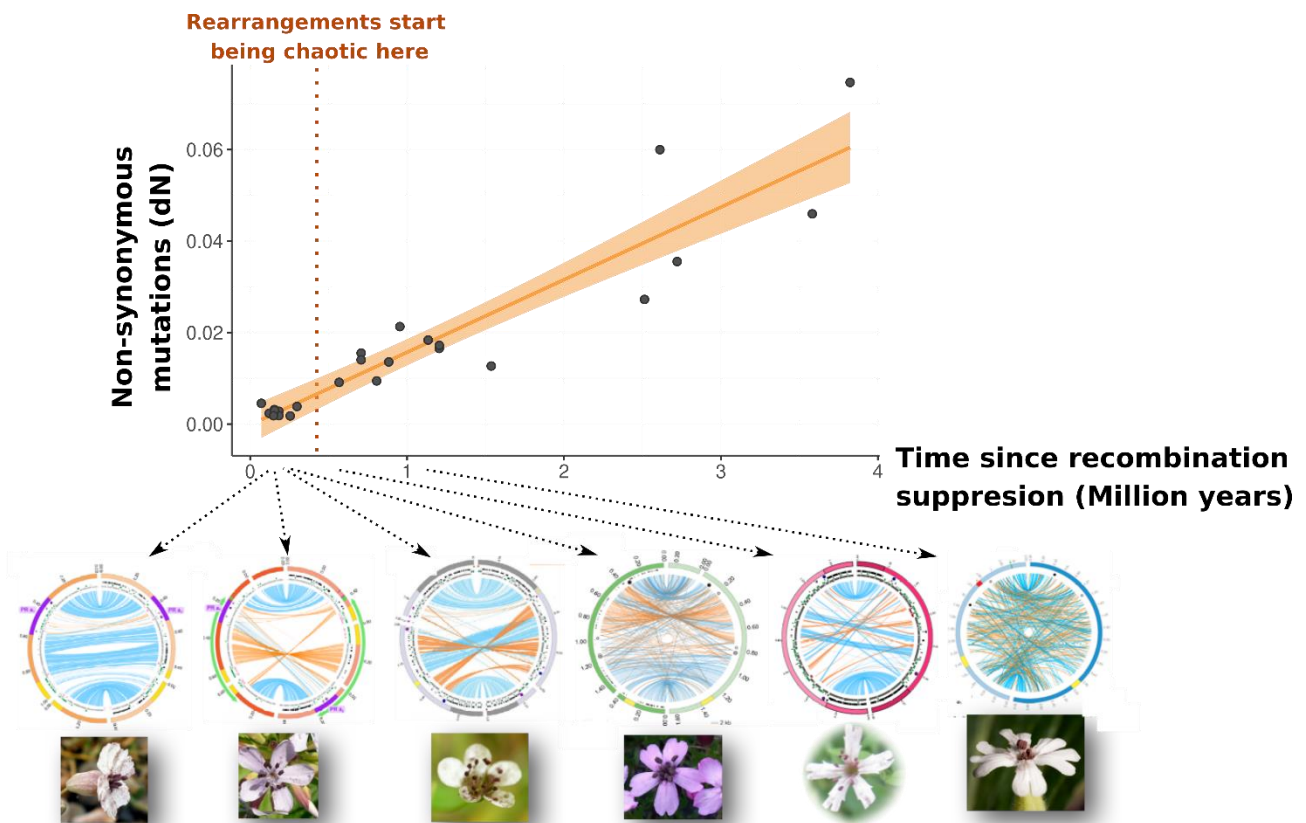
**g Rearrangement-constraint hypothesis**



**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).

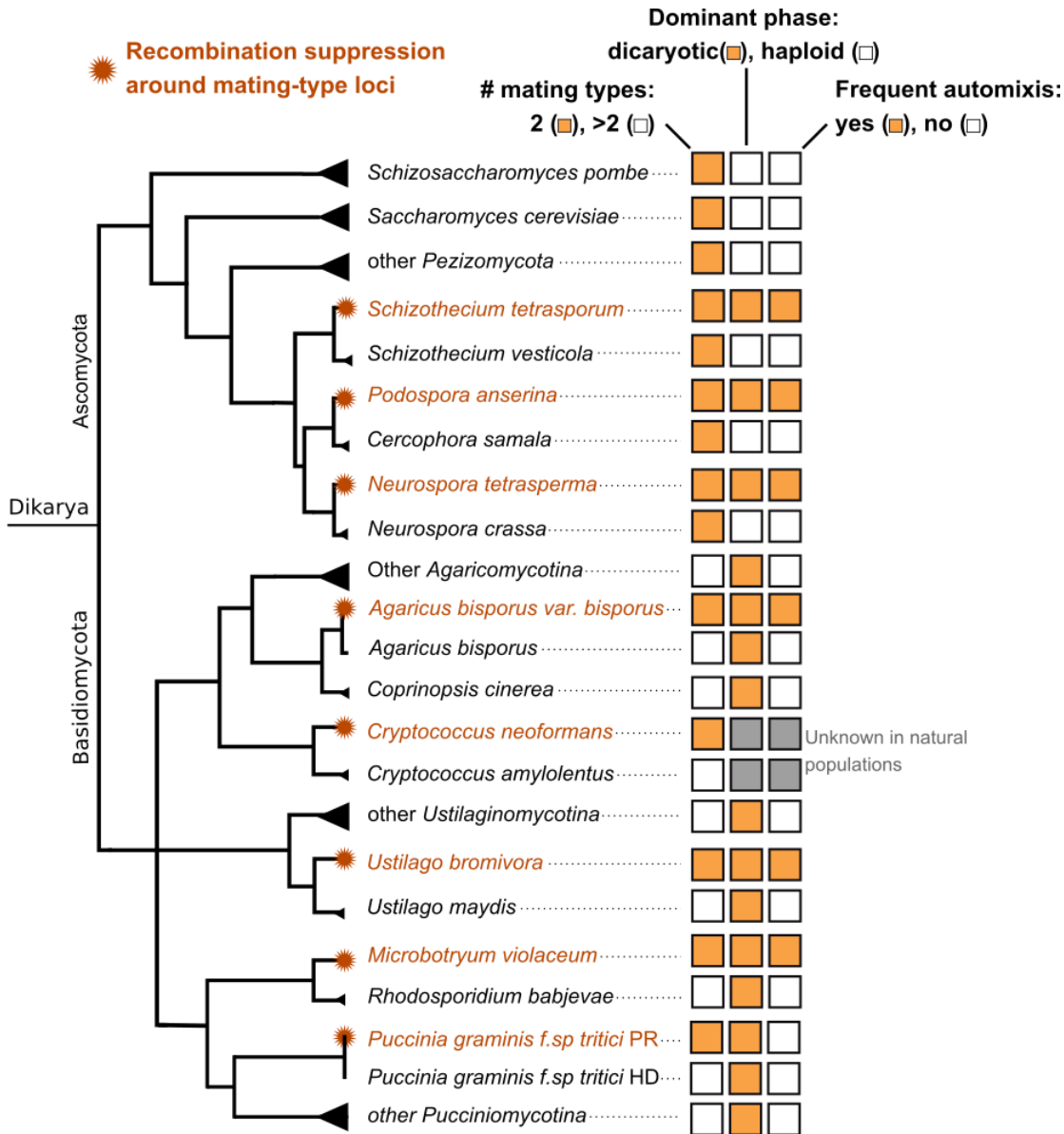


1015

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.