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The intricate relationship between sexually antagonistic selection and the evolution of sex chromosome fusions

Tomotaka Matsumoto [a,*], Jun Kitano [b]

[a] Division of Evolutionary Genetics, National Institute of Genetics, Yata 1111, Mishima, Shizuoka 411-8540, Japan
[b] Division of Ecological Genetics, National Institute of Genetics, Yata 1111, Mishima, Shizuoka 411-8540, Japan

HIGHLIGHTS

- We studied the evolutionary mechanisms of sex chromosome fusions theoretically.
- We focused on the effect of sexually antagonistic alleles on autosomes.
- We generated a simple one-locus model and conducted individual based simulations.
- Our results show that the evolutionary fate of the fusions is parameter sensitive.
- Stronger selection in females can cause the predominance of Y-autosome fusions.

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ABSTRACT

Sex chromosomes are among the most evolutionarily labile features in some groups of animals. One of the mechanisms causing structural changes of sex chromosomes is fusion with an autosome. A recent study showed that the establishment rates of Y chromosome–autosome fusions are much higher than those of other fusions (i.e., X-autosome, W-autosome, and Z-autosome fusions) in fishes and reptiles. Although sexually antagonistic selection may be one of the most important driving forces of sex chromosome–autosome fusions, a previous theoretical analysis showed that sexually antagonistic selection alone cannot explain the excess of Y-autosome fusions in these taxa. This previous analysis, however, is based on the assumption that sexually antagonistic selection is symmetric, sexually antagonistic alleles are maintained only by selection-drift balance (i.e., no supply of mutation), and only one type of fusion arises within a population. Here, we removed these assumptions and made an individual-based model to simulate the establishment of sex chromosome–autosome fusions. Our simulations showed that the highest establishment rate of Y-autosome fusion can be achieved when the fusion captures a rare male-beneficial allele, if the recurrent mutation rates are high enough to maintain the polymorphism of alleles with asymmetric, sexually antagonistic effects. Our results demonstrate that sexually antagonistic selection can influence the dynamics of sex chromosome structural changes, but the type of fusion that becomes the most common depends on fusion rates, recurrent mutation rates, and selection regimes. Because the evolutionary fate of sex chromosome–autosome fusions is highly parameter-sensitive, further attempts to empirically measure these parameters in natural populations are essential for a better understanding of the roles of sexually antagonistic selection in sex chromosome evolution.

1. Introduction

Sex chromosomes are among the most evolutionarily labile features in some groups of animals (Bachtrog et al., 2014; Beukeboom and Perrin, 2014; Bull, 1983; White, 1973). In some taxa such as fishes and reptiles, closely related species or even populations differ in sex chromosomes (Devlin and Nagahama, 2002; Ezaz et al., 2009; Kitano and Peichel, 2012). One of the mechanisms causing structural changes of sex chromosomes is a fusion between a sex chromosome and an autosome (White, 1973). Neo-sex chromosomes created by fusions are put under different evolutionary forces from those of autosomes (Bachtrog, 2006; Bachtrog et al., 2009; Charlesworth et al., 2005), can rapidly accumulate sex-biased genes (Yoshida et al., 2014; Zhou and Bachtrog, 2012) and potentially contribute to incipient speciation (Kitano et al., 2009). Although sex chromosomes were thought to be conserved

* Corresponding author.
E-mail address: tomotakamatsumoto2@gmail.com (T. Matsumoto).

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in soma taxa, such as mammals, recent genomic studies have revealed that sex chromosome–autosome fusions have occurred multiple times during the evolution of mammalian sex chromosomes (Veyrunes et al., 2008). Therefore, elucidation of the evolutionary forces driving sex chromosome–autosome fusions is essential for a better understanding of sex chromosome evolution.

Pennell et al. (2015) recently compiled empirical cases of sex chromosome–autosome fusions in vertebrates from the Tree of Sex database (The Tree of Sex Consortium, 2014). The researchers conducted a phylogenetic analysis and found that the establishment rate of Y-autosome fusions is much higher than that of other fusions (i.e., X-, W-, and Z-autosome fusions) in fishes and reptiles, whereas X-autosome and Y-autosome fusions are equally common in mammals (Yoshida and Kitano, 2012; Pennell et al., 2015). Furthermore, theoretical analyses have shown that the establishment rates of Y-autosome fusions become the highest among four types of fusion when (1) fusions are slightly deleterious and fusion rates are male-biased or (2) fusions are slightly deleterious and the effective population size is larger in female (Pennell et al., 2015).

Sexually antagonistic selection (selection acting in opposite directions in males and females) is one of the most important driving forces of sex chromosome evolution (Charlesworth et al., 2005; van Doorn and Kirkpatrick, 2007). Charlesworth and Charlesworth (1980) showed that the presence of a sexually antagonistic allele on the autosome can drive the fixation of sex chromosome–autosome fusions because the fusion of an autosome with a sexually antagonistic allele to a sex chromosome enables an allele that is beneficial in one sex to spend greater time in that sex (Charlesworth and Charlesworth, 1980). However, sexually antagonistic selection alone cannot explain the pattern that Y-autosome fusions are more prevalent than other types of sex chromosome–autosome fusions, unless the fusion rate is much higher in males than in females or males have a higher effective population size (Pennell et al., 2015), although the latter is rare (Bateman, 1948; Clutton-Brock, 1989). This prior theoretical analysis assumes that sexually antagonistic alleles are maintained by selection-drift balance without any recurrent mutation and that the magnitude of the selection coefficient is the same between males and females (i.e., sexually antagonistic selection is symmetric). In such a case, both male-advantageous (and female-detrimental) and female-advantageous (and male-detrimental) alleles would be maintained with equal frequency within a population. In contrast, if we allow the selection coefficients to differ between males and females (i.e., sexually antagonistic selection is asymmetric), either a male-advantageous (and female-detrimental) allele or a female-advantageous (and male-detrimental) allele would increase in a population, and another allele would be easily lost from the population in the absence of any mutational inputs. Because recurrent mutation is an important source of genetic variation (Radwan, 2008), it is necessary to examine how alleles with asymmetric, sexually antagonistic effects maintained by mutation-selection-drift balance would contribute to the establishment of sex chromosome–autosome fusions.

In this study, we established an individual-based model to simulate the evolution of sex chromosome–autosome fusions under sexually antagonistic selection on an autosomal locus. We extended the result in Pennell et al. (2015) and investigated how the selection regimes of sexually antagonistic selection influence the relative establishment rates of different sex chromosome–autosome fusions under different fusion rates and different recurrent mutation rates. Our results showed that if both of the fusion and mutation rates are high, a stronger sexually antagonistic selection in females than in males made the Y-autosome fusions the most prevalent. This pattern, however, disappeared when recurrent mutation rates contributing to polymorphism were low. These results indicate that the evolutionary fate of sex chromosome–autosome fusions is highly parameter-sensitive and, therefore, further attempts to empirically measure the levels of polymorphism and fitness effects of sexually antagonistic alleles in wild populations are important for a better understanding of the roles of sexually antagonistic selection in sex chromosome evolution.

2. Simulation model

The population consisted of equal numbers of reproductive females and males. We also assumed random mating between male and female individuals in the population: one individual of the next generation was the progeny of a randomly chosen male and a randomly chosen female. The population began with one pair of autosomes and one pair of sex chromosomes (either XY or ZW). The autosome was assumed to have a locus with two alleles under sexually antagonistic selection: allele A_m was assumed to have a higher relative fitness in males but a lower relative fitness in females, whereas another allele A_f was assumed to have a higher relative fitness in females but a lower relative fitness in males. The relative fitness types were:

Genotype:	A_mA_m	A_mA_f	A_fA_f
Male fitness:	$1+s_m$	$1+hs_m$	1
Female fitness:	1	$1+hs_f$	$1+s_f$

where s_m and s_f are sex-specific selection coefficients, and h is a dominance coefficient. This fitness model assumes that the intermediate expression of advantageous allele similarly affects the fitness of both male and female. Many previous studies have suggested that the relationship between gene expression and fitness is likely to be concave around the optimum (reviewed in Connallon and Clark, 2010). Based on these results, $h \geq 0.5$ may be a realistic parameter range for the above fitness model. The forward and backward mutation rates between A_m and A_f were assumed to be constant (u per generation). Fusions and fissions between sex chromosome and autosome were assumed to occur at the same rate F, and this rate was the same between males and females and the same for all of the four sex chromosomes. Recombination was assumed to be completely suppressed between paired chromosomes regardless of whether the fusion was heterozygous or homozygous.

We allowed for the possibility that fusions were deleterious because fusions often lead to loss of important genetic elements (Gardner et al., 2012). Fitness effects were assumed to be multiplicative so that unfused homozygotes, fusion heterozygotes, and fused homozygotes had a relative fitness $1:(1-s_{del}):(1-s_{del})^2$. An individual's total fitness was calculated as the product of the sexually antagonistic and deleterious fitness effects. In this study, we considered two s_{del} values, 0 and 0.01.

In the simulations, we assumed that the population size is constant with 1000 females and 1000 males and that the initial population harbored no fusion. The initial allele frequency of A_m and A_f at the autosomal locus was at equilibrium by mutation-selection-drift balance as determined by the recursion equations from a previous study (Connallon and Clark, 2012). We considered two mutation rates ($u=10^{-4}$ and 10^{-8}), to examine different polymorphism levels at the initial equilibrium. We initially conducted simulations with $F=10^{-4}$ because the estimated rates of Robertsonian fusions in humans are 10^{-3}–10^{-4} (Bandyopadhyay et al., 2002; Hamerton et al., 1975). This fusion rate, however, includes fusions between any pair of chromosomes. Because humans have 23 chromosome pairs, the number of combinations of pairs is

253 ($=_{23}C_2$). Therefore, the fusion rate between a particular autosome and a particular sex chromosome may be lower, so we also considered a lower fusion–fission rate $F=10^{-6}$ and compared the results between different fusion rates. Each simulation was run for 10^5 generations, and simulations were repeated 100 times for each combination of parameters. Because we assumed that one of XY or ZW sex determination system was fixed in the population, we simulated XY cases and ZW cases independently. In XY cases, sex chromosomes X and Y can fuse with an autosome and evolve simultaneously within a population. Similarly, Z and W can fuse with an autosome in ZW cases. Finally, we compared the frequencies of four types of sex chromosome–autosome fusions obtained from simulations in XY cases and ZW cases. Hereafter, Y–A, Y–A_m, and Y–A_f refer to Y-autosome fusion (regardless of linked alleles), and those linked to the male and female beneficial alleles, respectively. We employed a similar notation for X, Z, and W sex chromosomes.

3. Results

3.1. Simulations under a high fusion–fission rate and a high mutation rate

First, we considered the case with high fusion rates ($F=10^{-4}$) and high mutation rates ($u=10^{-4}$), and compared the establishment rates of four types of fusions (X–A, Y–A, Z–A, and W–A fusions). Here, we first examined cases with $h=0.5$ and $s_{del}=0$. In Fig. 1, we compare the time course of the average frequencies of four types of fusions under four different combinations of selection coefficients: $s_m=0$ and $s_f=0$ (no sexually antagonistic selection) (Fig. 1A); $s_m=0.1$ and $s_f=0.2$ (stronger sexually antagonistic selection in females) (Fig. 1B); $s_m=0.2$ and $s_f=0.1$ (stronger sexually antagonistic selection in males) (Fig. 1C); $s_m=0.2$ and $s_f=0.2$ (symmetric sexually antagonistic selection) (Fig. 1D).

In the absence of sexually antagonistic selection, all types of fusions evolved selectively neutrally and therefore, were established at similar rates (Fig. 1A). In the presence of stronger sexually antagonistic selection in females, Y–A fusion exhibited the fastest increase (Fig. 1B). Under this condition, stronger sexually antagonistic selection in females makes the female-beneficial allele A_f common within a population, whereas the male-beneficial allele A_m becomes rare and is maintained at a very low frequency by mutation-selection-drift balance. Therefore, once a Y–A fusion can capture such a rare allele A_m, the relative fitness of males with Y–A_m fusions is expected to become very high compared with that of other males who are likely to carry the common allele A_f. In contrast, under stronger selection in males, allele A_f becomes rare; therefore the W-A_f could have high relative fitness and exhibited the fastest increase (Fig. 1C). In this case, allele A_m becomes common within a population and a large proportion of males in a population can have allele A_m without Y–A fusions. Therefore the advantage of Y–A_m fusion became smaller compared with that in Fig. 1B and showed slower increase (Fig. 1C).

Interestingly, in the presence of sexually antagonistic selection, the frequencies of X–A or Z–A fusion did not reach the levels of Y–A or W–A fusion, respectively, even after 100,000 generations (Fig. 1B–D). This is surprising because X–A and Z–A fusions can also capture female- and male-beneficial alleles, respectively, and may be adaptive. The result under symmetric sexually antagonistic selection (Fig. 1D) was particularly inconsistent with the results of Pennell et al. (2015), which indicated equal establishment rates of four types of fusion if sexually antagonistic selection is symmetric. This difference might result from the interacting effect between different types of fusion evolving simultaneously within a single population. This effect was not considered in Pennell et al. (2015) and we will discuss later in more detail.

When we assumed that fusions were slightly deleterious ($s_{del}=0.01$), the differences among types of fusion became more apparent. When sexually antagonistic selection was asymmetric (stronger sexually antagonistic selection in one sex), only one type of fusion showing the fastest increase in the absence of deleterious effects of fusions became established (Fig. 1F and G). These results show that the advantageous effects of capturing the rare allele A_m (allele A_f) is strong and can overcome the deleterious effects of fusions, and allow only Y–A (W–A) fusion to evolve in a population.

In Fig. 2, we explored much wider ranges of s_f and s_m in XY systems assuming no deleterious effects of fusions. Fig. 2 shows the establishment rates of fusions in which the frequencies of the X–A fusion (Fig. 2A) and Y–A fusion (Fig. 2B) became higher than 0.9 within a population. Consistent with the results in Fig. 1B, when $s_f > s_m$, Y–A fusion showed a higher establishment rate than X–A fusion did (under the diagonal in Fig. 2B). When the asymmetry of s_m and s_f was very large ($s_m=0.001$ and $s_f \geq 0.01$), however, the establishment rate of Y–A fusion was not very high. This might be because under conditions where $s_f \gg s_m$, the frequency of allele A_m maintained by mutation-selection-drift balance became very low, and therefore the emergence rate of Y–A_m fusions became very low. Because the establishment rates of fusions largely depend on their emergence rates, the condition $s_f \gg s_m$ decreases the establishment rate of Y–A_m fusion. Similar results were obtained for the ZW sex determination system and are shown in Supplementary Fig. 1A and B.

3.2. Simulations under a high fusion–fission rate and a low mutation rate

Second, we considered the cases with $F=10^{-4}$ and $u=10^{-8}$. The lower mutation rate makes the maintenance of polymorphism within a population more difficult, particularly when selection coefficients in females and males are asymmetric. In such a case, the emergence rate of fusions capturing rare beneficial alleles would become very low, making the establishment rates of Y–A and W–A fusions much lower under $s_f > s_m$ and $s_f < s_m$, respectively. As a result, the average frequencies of four types of fusions became approximately the same (Fig. 3A–C). A comparison among Fig. 3A–C indicates that the fusions evolved almost neutrally under asymmetric sexually antagonistic selection with low mutation rates (Fig. 3B and C). When fusions were slightly deleterious, they rarely became established (Fig. 3E–G). Only under symmetric sexually antagonistic selection, Y–A (W–A) fusions could be established at a higher probability than those of the neutral case because the equal selection coefficients in females and males could maintain the polymorphism of sexually antagonistic alleles A_m and A_f (Fig. 3D and H). Under symmetric sexually antagonistic selection, the relative fitness of Y–A_m (W–A_f) fusion would not be as high as that under $s_m < s_f$ ($s_m > s_f$), because the frequency of allele A_m (allele A_f) is expected to be 0.5 and not very rare within a population. However, its relative fitness may still be high because male (female) with the fusion can avoid the risk of having a disadvantageous allele A_f (allele A_m) whose frequency is also 0.5. Thus, the fusion could rapidly increase within a population. As in the previous case with the high mutation rate, Y–A (W-A) fusions more readily became established than X–A (Z–A) fusions did (Fig. 3D and H). Fig. 4 shows the establishment rates of X–A and Y–A under the assumption of $h=0.5$ and $s_{del}=0$. In contrast to Fig. 2, the establishment rates of fusions substantially dropped unless sexually antagonistic selection was symmetric and strong ($s_m=s_f \geq 0.05$). Similar results were obtained for the ZW sex determination system and are shown in Supplementary Fig. 1C and D.

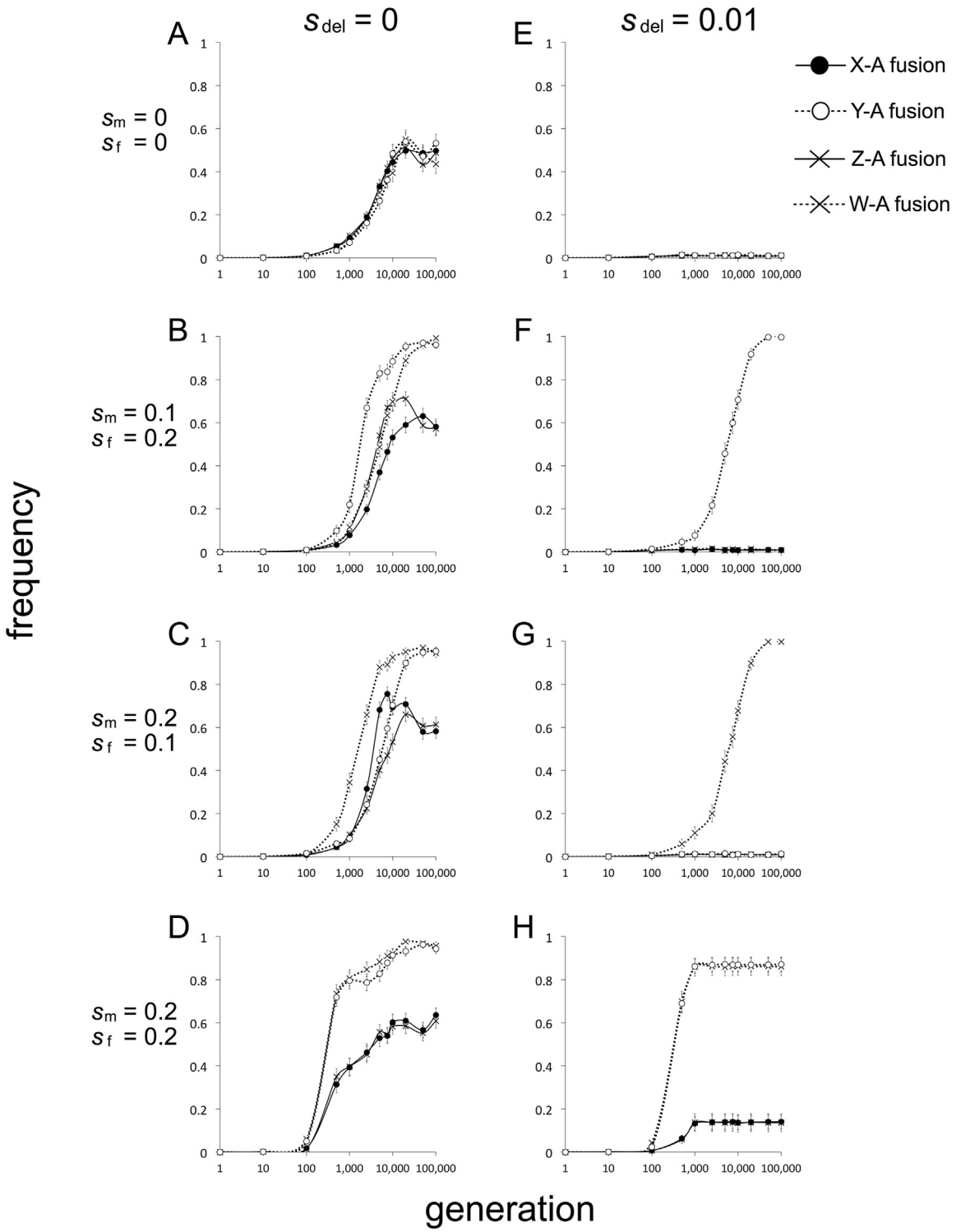

Fig. 1. The time course of the frequencies of four types of fusions under a variety of combinations of sexually antagonistic selection and deleterious effects of fusions in $F=10^{-4}$, $u=10^{-4}$ and $h=0.5$. (A)–(D) show the results in $s_{del}=0$ and (E)–(G) show the results in $s_{del}=0.01$. (A) and (E) show the results in $s_m=0$, $s_f=0$. (B) and (F) show the results in $s_m=0.1$, $s_f=0.2$. (C) and (G) show the results in $s_m=0.2$, $s_f=0.1$. (D) and (H) show the results in $s_m=0.2$, $s_f=0.2$. The simulation was replicated 100 times in each parameter set, and the average and standard error are shown in this figure. The different line colors and styles show the different types of fusion.

3.3. Simulations under a low fusion–fission rate

Next, we considered the case with $F=10^{-6}$ to examine how the reduced fusion–fission rate affects the results. In Figs. 5 and 6, we show the time course of the average frequencies of the fusions under a high and a low mutation rate, respectively. The average frequencies of fusions in the low fusion–fission rate were decreased compared to those in the high fusion–fission rate (Figs. 1–4). When the mutation rate was high (i.e., polymorphism of sexually antagonistic alleles can be easily maintained) and sexually antagonistic selection was stronger in females (Fig. 5B), Y–A_m and Z–A_m fusions could have high relative fitness and as a result, Y–A and Z–A fusions became more common than X–A and W–A fusions. In this case, the average frequency of Z–A fusions

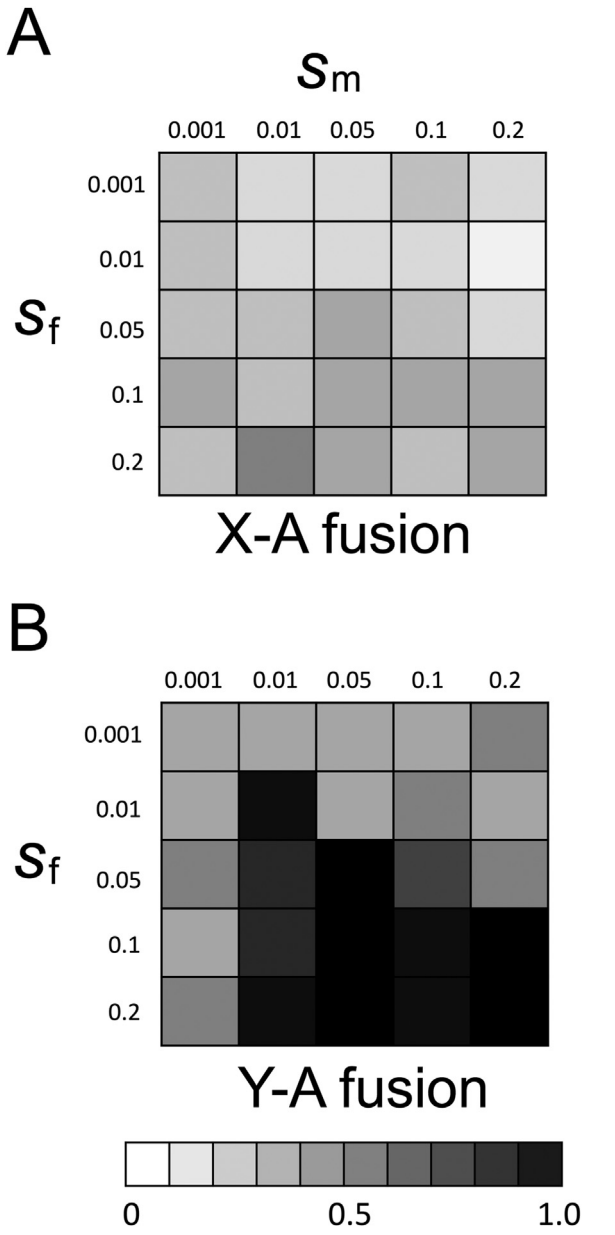

Fig. 2. The probability of the evolution of X–A and Y–A fusion in $F=10^{-4}$, $u=10^{-4}$ and $h=0.5$, assuming no deleterious effect of fusion ($s_{del}=0$). (A) shows the probability in which the frequency of X–A fusion became greater than 90% in a population after 10^5 generations and (B) shows the same for Y–A fusion. The simulation was replicated 100 times in each parameter set, and the probability is expressed in gray scale.

became similar to that of Y–A fusions (Fig. 5B). When the selection coefficients were equal in females and males, all four types of fusion showed the similar frequencies (Fig. 5D). In contrast to the high fusion–fission rate case, the result in Fig. 5D is consistent with that of Pennell et al. (2015). Similar to the high fusion–fission rate case, slightly deleterious effects of fusions ($s_{del}=0.01$) made the frequencies of Y–A (W–A) higher than those of X–A (Z–A) (Fig. 5F–H). When the mutation rate was low, the frequencies of four types of fusion became similar under all cases of the sexually antagonistic selection without the deleterious effects of fusions (Fig. 6).

Figs. 7 and 8 show the establishment rates of the X–A and Y–A fusions assuming $F=10^{-8}$, $h=0.5$ and $s_{del}=0$. In the high mutation rate case, the establishment rate of X–A and Y–A fusions became slightly higher when $s_m > s_f$ and $s_f > s_m$, respectively (Fig. 7). These results were consistent with those in Fig. 5B and C. When the mutation rate was low, as seen in the high fusion–fission rate case (Fig. 4), low polymorphism of sexually antagonistic alleles caused almost neutral evolution of the fusions (Fig. 8). In both cases of the high and the low mutation rates, the establishment rates of the fusions became the highest in $s_m=s_f$ because the polymorphism could be maintained easily and there should be sufficient opportunity for which the fusion to capture the beneficial allele, even if the fusion rate was low. The result in the ZW sex determination system were also consistent with those in Figs. 5 and 6 (data not shown).

3.4. Other factors affecting the fusion evolution

We have thus far focused on the effects of mutation rates, fusion–fission rates, and selection coefficients. Finally, we examined three other factors that might affect the establishment rates of the four types of fusion.

First, we examined the effects of the degree of dominance. Although all of the analysis thus far assumed $h=0.5$, different values of h would affect the maintenance of the polymorphism of sexually antagonistic alleles and therefore, have substantial effects on the establishment of fusions. We considered two extreme cases, $h=0$ and $h=1$. In Supplementary Fig. 2, we show the results of the XY sex determination system under $F=10^{-4}$. The calculation of the equilibrium allele frequencies under sexually antagonistic selection in Connallon and Clark (2012) is applicable only for the cases with the disadvantageous allele being recessive or additive (i.e., h is between 0.5 and 1 in our model). Therefore, we considered only the cases with selection coefficients being equal in females and males, where the equilibrium allele frequency became 0.5 for each allele. As shown in Supplementary Fig. 2, when $h=0$, the establishment rates of both of X–A and Y–A fusions decreased. This is because the maintenance of the polymorphism in the heterozygote became difficult. In contrast, when $h=1$, the polymorphism became easier to maintain and the establishment rates of fusions became high. However, the establishment rates did not become much higher than those under $h=0.5$. This result suggests that $h=0.5$ is sufficient to maintain the polymorphism for the establishment of the fusions under $F=10^{-4}$ and a further increase of the polymorphism does not have a large impact on the establishment rate of the fusion.

Second, we examined the effect of female meiotic drive. In humans, female meiotic drive is known to preferentially transmit a fused chromosome to eggs rather than to polar bodies, and the estimates of the transmission bias of fused chromosomes is often as high as 1.4 compared to those of unfused chromosomes (Pardo-Manuel and Sapienza 2001). To incorporate this factor, we modified the model such that the ratio of a heterozygous female carrier of a fusion transmitting the fused and unfused chromosomes to an egg was 1.4:1. In Supplementary Fig. 3, we show the time course of the average frequency of X–A and Y–A fusions under $F=10^{-4}$. In contrast to Fig. 1, X–A fusions could rapidly increase and became fixed within a population in the presence of female meiotic drive. This favored fusions regardless of whether there is sexually antagonistic selection or not.

Third, we examined the effects of unequal effective population sizes between males and females. As mentioned in Pennell et al. (2015), sexual selection tends to make effective population sizes of males smaller than those of females, known as Bateman's principle (Bateman, 1948). Additionally, it is known that the efficiency of selection largely depends on effective population sizes (Crow and Kimura, 1970; Ohta, 1973). Pennell et al. (2015) suggested that if fusions are slightly deleterious and male effective population size is smaller than that of female, only Y–A fusions can evolve in a population, which is due to the higher efficiency of genetic drift fixing slightly deleterious mutations in populations with smaller population sizes (Ohta, 1973). We confirmed these suggestions in

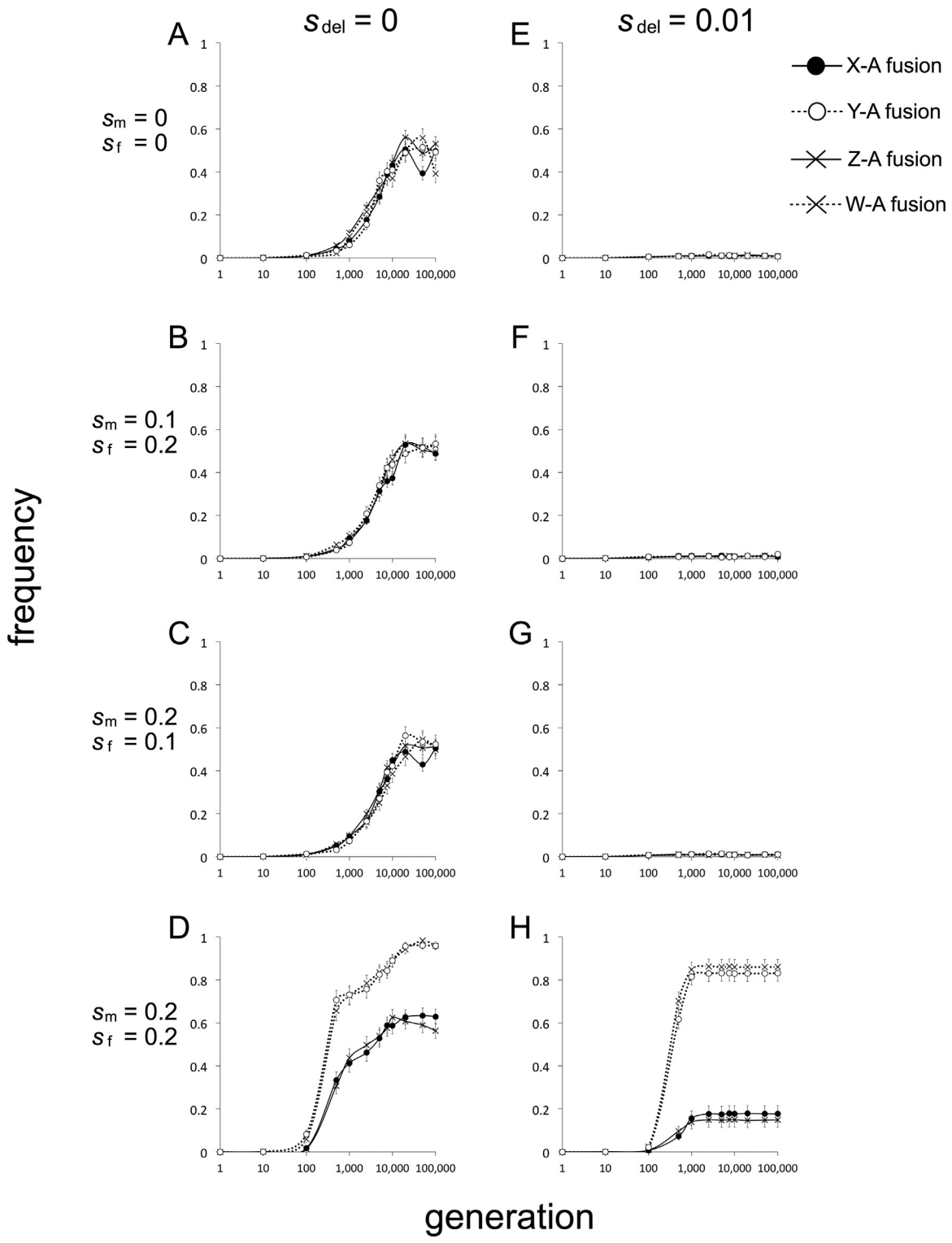

Fig. 3. The time course of the frequencies of four types of fusions under a variety of combinations of sexually antagonistic selection and deleterious effects of fusions in $F=10^{-4}$, $u=10^{-8}$ and $h=0.5$. The values of the selection coefficients used in each panel are the same as those in Fig. 1. The simulation was replicated 100 times in each parameter set, and the average and standard error are shown in this figure. The different line colors and styles show the different types of fusion.

our simulations by reducing the male population size to 100 while maintaining the female population size at 1000. The results are shown in Supplementary Fig. 4. As expected, if fusions are slightly deleterious and males have smaller effective population sizes than females do, only Y–A fusions could evolve in a population in the absence of sexually antagonistic selection (Supplementary Fig. 4C and D). Similarly, as expected, under sexually antagonistic selection, the reduced male population size decreased the establishment rate of Y–A fusion (compare Supplementary Figs. 4B and 2B). The decreased establishment rate of Y–A fusion increased the establishment rate of X–A fusion (compare Supplementary Figs. 4A and 2A), which may be due to the interacting effects of fusions discussed later.

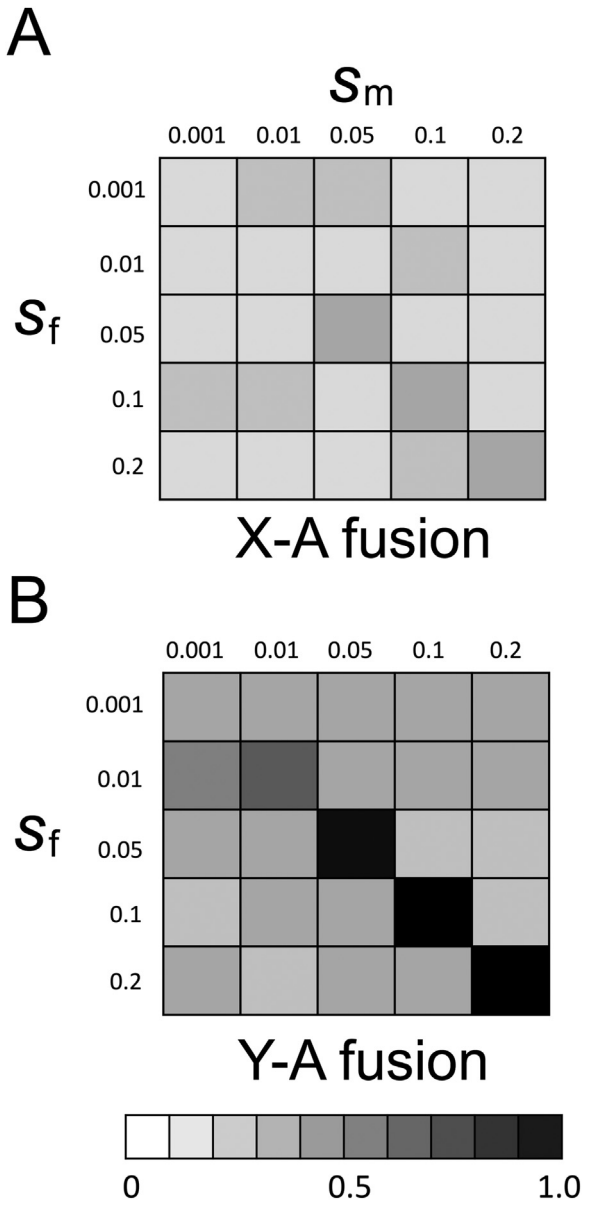

Fig. 4. The probability of the evolution of X–A and Y–A fusion in $F=10^{-4}$, $u=10^{-8}$ and $h=0.5$, assuming no deleterious effect of fusion ($s_{del}=0$). (A) shows the probability in which the frequency of X–A fusion became greater than 90% in a population after 10^5 generations and (B) shows the same for Y–A fusion. The simulation was replicated 100 times in each parameter set, and the probability is expressed in gray scale.

4. Discussion

4.1. Advantage of capturing a rare beneficial allele

Our individual-based simulations showed that sexually antagonistic selection contributes to sex chromosome structural changes. However, the evolutionary dynamics of sex chromosome–autosome fusions largely depended on the fusion rates, recurrent mutation rates, and selection regimes.

Our main focus in this study was the condition in which the selection coefficients in males and females were unequal. When sexually antagonistic selection is stronger in females than that in males, male beneficial alleles become rare in a population. In such a case, males with Y–A fusions that capture the rare male-beneficial allele are expected to have relatively higher fitness than the majority of other males who are unlikely to carry male-beneficial alleles because of the low frequencies of these alleles. This may seem to be counterintuitive as one may expect that stronger selection in males increases the advantage of Y–A fusions leading to a higher establishment rate of these fusions. However, stronger selection in males than in females makes the male beneficial alleles common in a population, so males lacking the fusion are also likely to carry the male beneficial alleles with high probability and males with Y–A fusions capturing the male beneficial allele do not necessarily have higher fitness.

Although fusions capturing a rare beneficial allele can have high fitness in a population, asymmetry of selection coefficients makes the polymorphism of sexually antagonistic alleles easily lost from the population without any substantial mutational inputs. Consistent with this idea, when the mutation rate was low, the establishment rates of Y–A fusion reduced when the selection coefficients were asymmetric, but not when the selection coefficients were symmetric (Fig. 4B and Supplementary Fig. 1D). Reduction in fusion–fission rates also reduced the establishment rates of Y–A fusions especially when the selection coefficients were asymmetric. This is likely because the probability of capturing rare beneficial alleles before they are lost from the population is very low under the low fusion–fission rate.

4.2. Interactions between different types of fusions simultaneously evolving within a population

If the selection regime is symmetric, the fixation probabilities of the four types of fusion are expected to be similar because X–A (Z–A) fusions have an occurrence rate that is three times higher, so the differences in fixation probabilities can be canceled out (Pennell et al., 2015). Contrary to this expectation, we found that Y–A (W–A) fusions showed the faster increase and higher establishment rate in the population than X–A (Z–A) fusions did under high fusion–fission rates (Figs. 1D and 3D). If the fusion rate is high, multiple fusions can emerge within a very short time interval (when $F=10^{-4}$, one X–A (Z–A) fusion and one Y–A (W–A) fusion are expected to occur every 3.3 and 10 generations, respectively) and can coexist within a population. In such a case, the contribution of the higher occurrence rate of X–A (Z–A) fusions to the higher establishment rate may decrease. Therefore, Y–A (W–A) fusions capturing male- or female-beneficial alleles can increase in the population more rapidly than X–A (Z–A) fusions can because of their greater advantageous effects compared to X–A (Z–A) fusions.

The faster increase of Y–A (W–A) fusions than X–A (Z–A) fusions may further suppress the establishment of X–A (Z–A) fusions. In our simulations, we assumed that the fusions completely suppress recombination between paired chromosomes. Thus, while Y–A (W–A) fusions initially increase their frequencies, the advantageous effects of X–A (Z–A) fusions would accordingly disappear in males (females) because Y–A (W–A) fusions alone can suppress recombination in males (females). These interacting effects between fused chromosomes would suppress the establishment of X–A (Z–A) fusions, even if they are advantageous, and create the differences between the average frequencies of Y–A (W–A) and X–A (Z–A) fusions after 100,000 generations, as shown in Figs. 1D and 3D. This interacting effect of fusions might also make the different dynamics between X–A and Z–A fusions in the asymmetric selection regime (Fig. 1B and C). Because Y–A (W–A) showed the fastest increase, the interacting effect suppressed the increase of X–A (Z–A). We confirmed that if we assume only one type of fusions can emerge within a population, all four types of fusions showed the similar average frequencies after 100,000 generations under symmetric sexually antagonistic selection and high fusion–fission rate (data not shown).

When the fusions were slightly deleterious, all of these differences became more apparent. For example, in one combination of

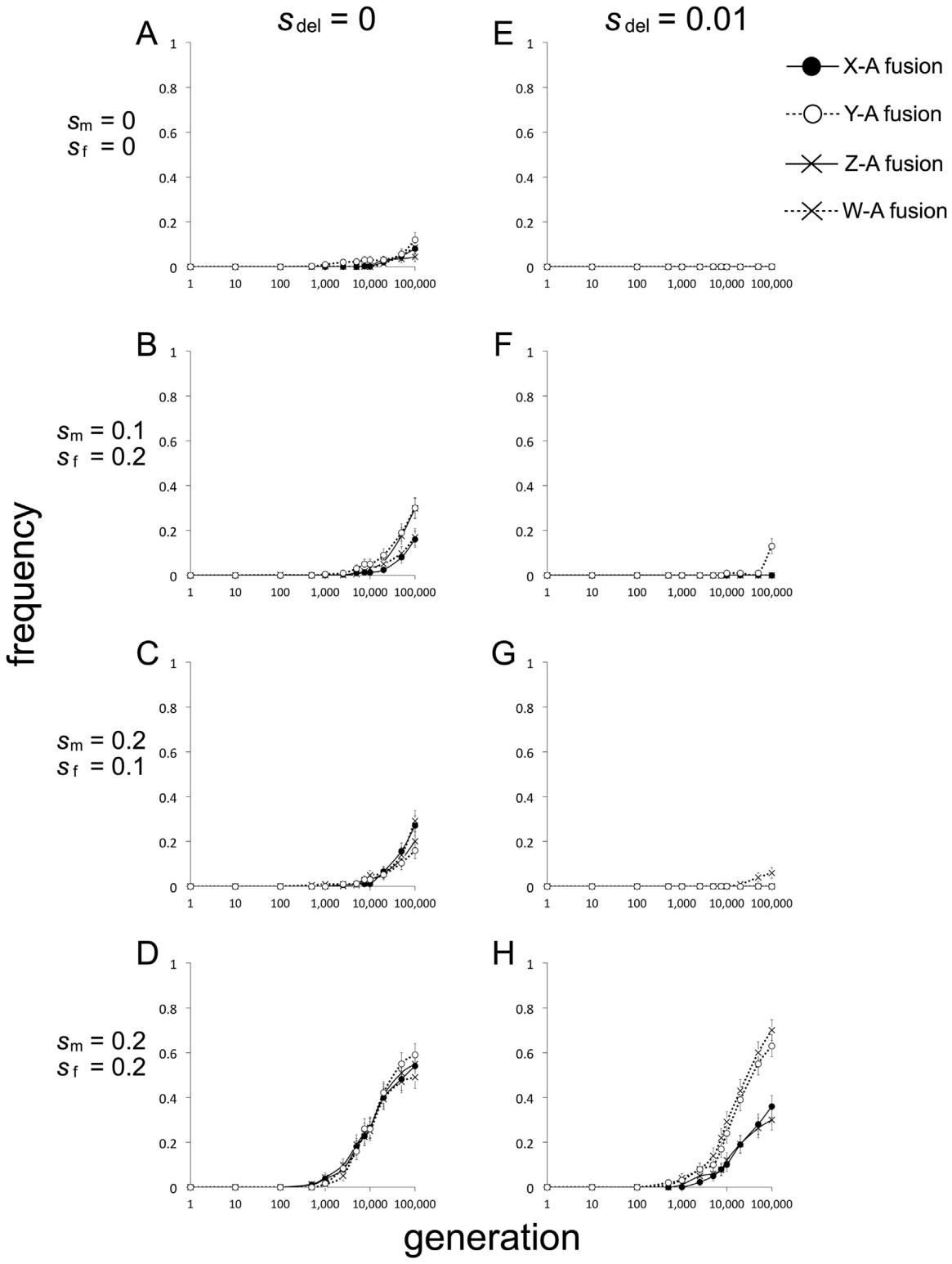

Fig. 5. The time course of the frequencies of four types of fusions under a variety of combinations of sexually antagonistic selection and deleterious effects of fusions in $F=10^{-6}$, $u=10^{-4}$ and $h=0.5$. The values of the selection coefficients used in each panel are the same as those in Fig. 1. The simulation was replicated 100 times in each parameter set, and the average and standard error are shown in this figure. The different line colors and styles show the different types of fusion.

parameters, only Y–A and W–A fusions could evolve (Fig. 1F and G). This may be because Y–A or W–A fusions never become homozygotes, which should have lower fitness than the heterozygotes do in terms of the effects of s_{del}. This enables Y–A and W–A fusions to have higher relative fitness than X–A and Z–A fusions. If a fixation of X–A (Z–A) fusions occurs before that of Y–A (W–A) fusions, the interacting effect of the fusions suppresses the increase of Y–A (W–A) fusions because X–A (Z–A) fusions alone can suppress recombination in males (females). The reduced fitness of X–A (Z–A fusions) by the deleterious effect of the fusions reduces this interacting effect and thus, increases the establishment rate of Y–A (W–A) fusions. As shown in Supplementary Fig. 4B and D, the

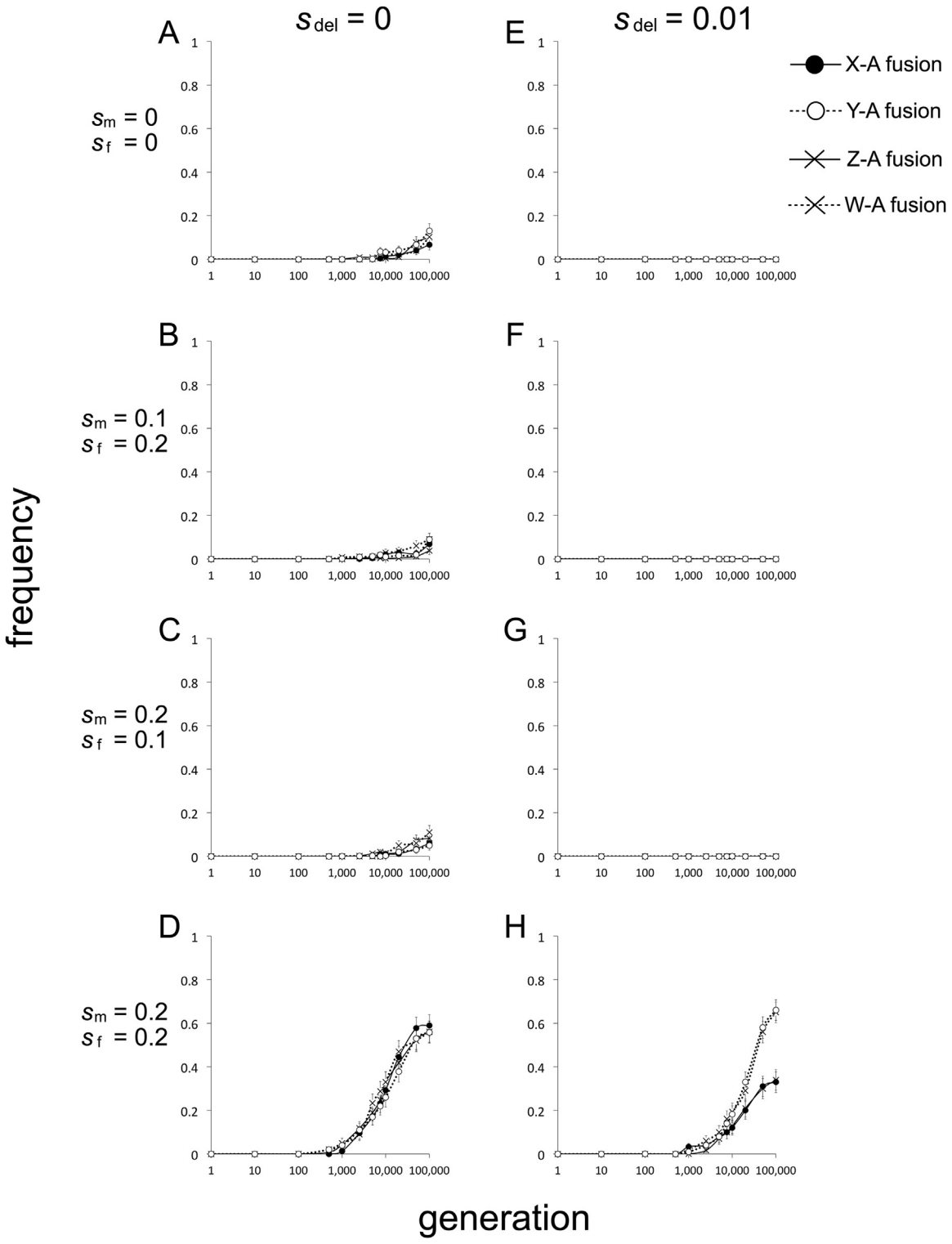

Fig. 6. The time course of the frequencies of four types of fusions under a variety of combinations of sexually antagonistic selection and deleterious effects of fusions in $F=10^{-6}$, $u=10^{-8}$ and $h=0.5$. The values of the selection coefficients used in each panel are same as those in Fig. 1. The simulation was replicated 100 times in each parameter set, and the average and standard error are shown in this figure. The different line colors and styles show the different types of fusion.

slightly deleterious effect of the fusions increased and decreased the establishment rates of Y–A and X–A compared to the case with in $s_{del}=0$ when selection on the autosomal locus was strong. This would also contribute to the high average frequency of Y–A (W–A) fusions shown in Fig. 1 and the following results. Note that when the fusions were highly deleterious ($s_{del}=0.1$), the deleterious effect became stronger than the advantageous effect of the fusions and the evolution of fusions became impossible (Supplementary Fig. 4E and F).

Because sex chromosomes differ in the time spent in females, female meiotic drive favoring fusions also resulted in differences in the establishment rates of different types of fusions. As shown in Fig. 1B, in the absence of female meiotic drive, the rapid increase in Y–A fusions suppressed the increase in X–A fusions through the

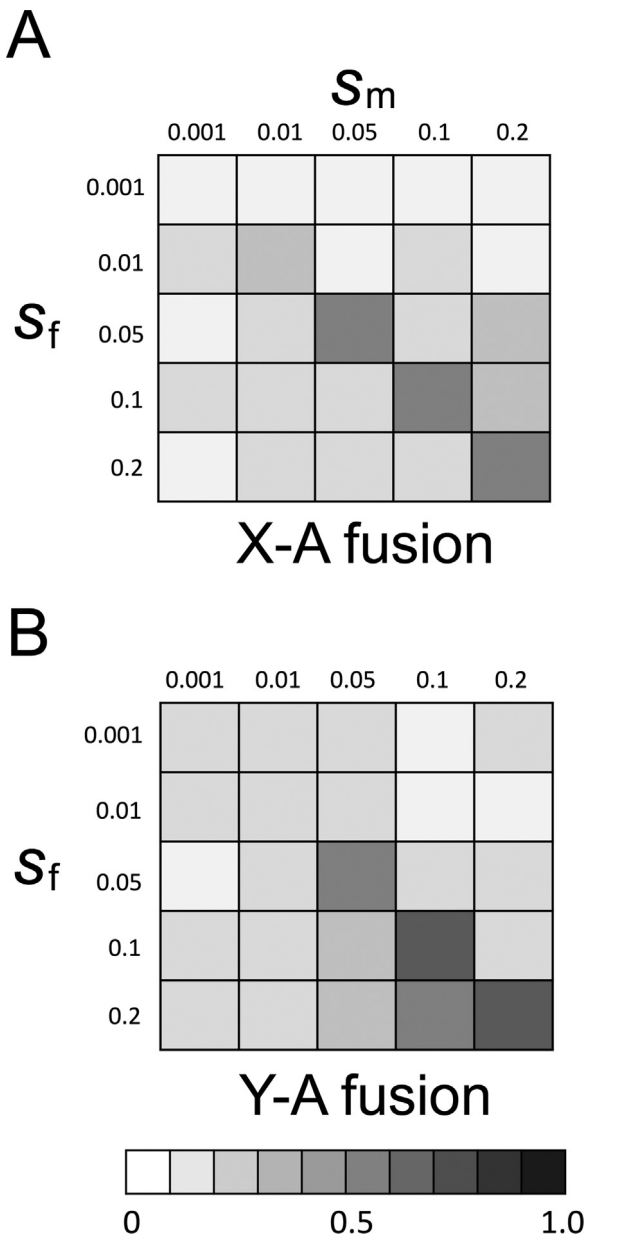

Fig. 7. The probability of the evolution of X–A and Y–A fusion in $F=10^{-6}$, $u=10^{-4}$ and $h=0.5$, assuming no deleterious effect of fusion ($s_{del}=0$). (A) shows the probability in which the frequency of X–A fusion became greater than 90% in a population after 10^5 generations and (B) shows the same for Y–A fusion. The simulation was replicated 100 times in each parameter set, and the probability is expressed in gray scale.

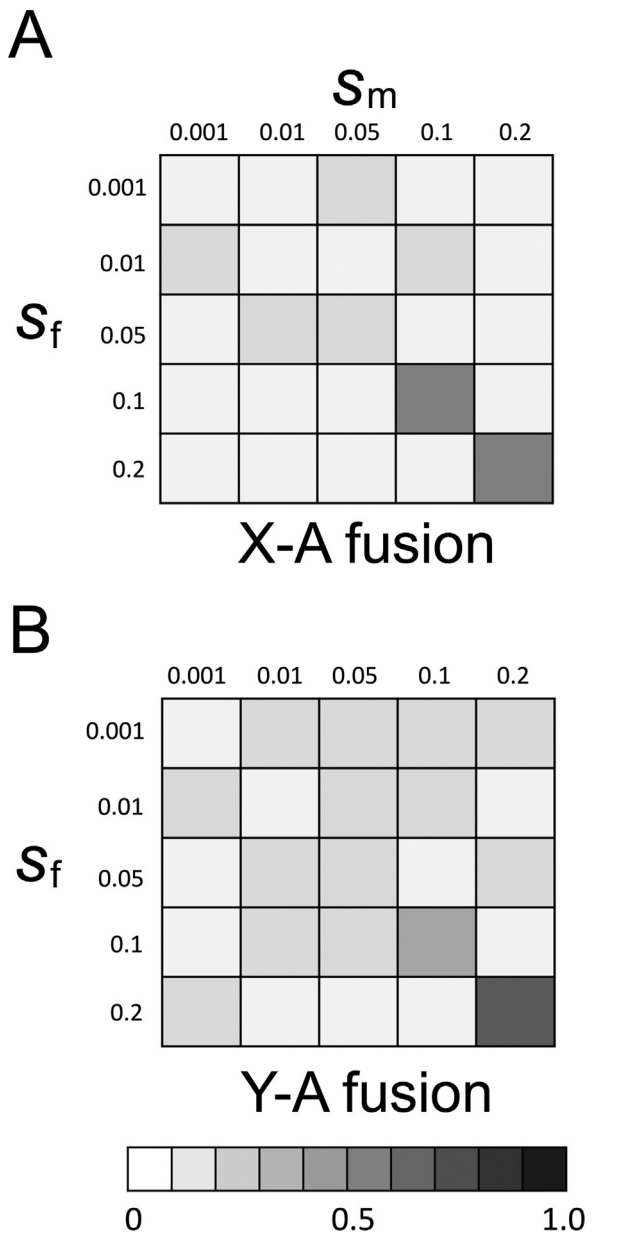

Fig. 8. The probability of the evolution of X–A and Y–A fusion in $F=10^{-6}$, $u=10^{-8}$ and $h=0.5$, assuming no deleterious effect of fusion ($s_{del}=0$). (A) shows the probability in which the frequency of X–A fusion became greater than 90% in a population after 10^5 generations and (B) shows the same for Y–A fusion. The simulation was replicated 100 times in each parameter set, and the probability is expressed in gray scale.

interacting effect of fusions when $s_m=0.1$ and $s_f=0.2$. Oppositely, in the presence of female meiotic drive, the rapid increase in X–A fusions decreased the advantage of Y–A fusions in males and suppressed the fixation of Y–A fusions (Supplementary Fig. 3).

4.3. Assumptions in the model

We will briefly discuss the effects of three assumptions that may affect our results. First, we assumed that the fusion–fission rates are the same for all of the four sex chromosomes. If fusion rates differ among the sex chromosomes as proposed by Pennell et al. (2015), this may affect the differences in the establishment rates of different sex chromosomes. Second, we assumed that sex chromosome–autosome fusions completely suppress recombination between paired chromosomes even in the heterozygous state. If we assume that heterozygotes of fusions have a weak recombination as the model of autosome-autosome fusions suggests in Guerrero and Kirkpatrick (2014), this makes the effects of the interaction between different fusions (e.g., X–A and Y–A fusions) small and may increase the probability of the evolution of X–A and Z–A fusions. Investigating the effects of recombination rates on the evolution of four types of fusions would be an interesting topic for future studies. Third, we assumed that the initial allele frequency was at the equilibrium calculated by Connallon and Clark (2012). If we allow more polymorphism at the beginning of the simulation, the probability of which a sex chromosome–autosome fusion can capture the beneficial allele would increase, and therefore, the probability of the evolution of the fusion would also increase. However, considering that the allele frequency can quickly approach the equilibrium in the simulation as the selection becomes

strong, the effect of this initial polymorphism on the probability of the evolution of the fusion may not be very strong.

4.4. Biological implications

Our results showed that asymmetric sexually antagonistic selection can promote conditions in which the establishment rate of Y–A fusion becomes much higher than that of the other three types of fusions, suggesting that the biased Y–A fusion reported in Pennell et al. (2015) can be explained by asymmetric sexually antagonistic selection (Fig. 2 and Supplementary Fig. 1A and B).

Polymorphism of sexually antagonistic alleles has been widely observed and the selection coefficients often differ between males and females (Chippindale et al., 2001; Innocenti and Morrow, 2010; Johnston et al., 2013; Connallon et al., 2010). Although it is not clear whether fishes and reptiles tends to have higher selective coefficients in females than in males, future studies addressing this question would greatly improve our understanding of the contribution of sexually antagonistic selection to the evolution of Y–A fusions in natural populations.

Although we do not know what the actual mutation rates of sexually antagonistic genes would be, a gene flow from other populations with different regimes of sexually antagonistic selection may also provide polymorphism of sexually antagonistic alleles. For example, a certain male trait, such as male nuptial color, may be favored in one environment, but disfavored in another environment (Boughman, 2001; Seehausen et al., 2008). If there is a gene flow between two populations inhabiting contrasting environments, polymorphism can be maintained by migrants. These findings suggest that sex chromosome–autosome fusions may be common in contact zones between populations adapting to different environments.

5. Conclusions

As theory suggested, our simulations demonstrate that sexually antagonistic selection can influence the dynamics of sex chromosome structural changes. However, the type of fusion that becomes most common depends on fusion rates, recurrent mutation rates, and selection regimes. Because the evolutionary fate of sex chromosome–autosome fusions is highly parameter-sensitive, further attempts to empirically measure these parameters in natural populations are essential for a more thorough understanding of the roles of sexually antagonistic selection in sex chromosome structural changes.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jtbi.2016.05.036.

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