International Institute for
Applied Systems Analysis
Schlossplatz 1
A-2361 Laxenburg, Austria

Tel: +43 2236 807 342
Fax: +43 2236 71313
E-mail: publications@iiasa.ac.at
Web: www.iiasa.ac.at

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Masato Yamamichi
Akira Sasaki (sasaki@iiasa.ac.at)

Approved by

Ulf Dieckmann
Director, Evolution and Ecology Program

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Single-gene speciation with pleiotropy: Effects of allele dominance, population size, and delayed inheritance

Masato Yamamichi*[1], Akira Sasaki[¶2,3]

1) Department of Ecology and Evolutionary Biology, Cornell University, Ithaca, NY 14853, USA

2) Department of Evolutionary Studies of Biosystems, Graduate University for Advanced Studies (Sokendai), Hayama, Kanagawa, 240-0193, Japan

3) Evolution and Ecology Program, International Institute for Applied System Analysis, A-2361, Laxenburg, Austria

*corresponding author: my287@cornell.edu, Phone: +1-607-254-4231

¶: sasaki_akira@soken.ac.jp, Phone: +81-46-858-1537

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ABSTRACT

Single-gene speciation is considered to be unlikely, but an excellent example is found in land snails, in which a gene for left-right reversal has given rise to new species multiple times. This reversal might be facilitated by their small population sizes and maternal effect (i.e., 'delayed inheritance', in which an individual's phenotype is determined by the genotype of its mother). Recent evidence suggests that a pleiotropic effect of the speciation gene on anti-predator survival may also promote speciation. Here we theoretically demonstrate that, without a pleiotropic effect, in small populations the fixation probability of a recessive mutant is higher than a dominant mutant, but they are identical for large populations and sufficiently weak selection. With a pleiotropic effect that increases mutant viability, a *dominant* mutant has a higher fixation probability if the strength of viability selection is sufficiently greater than that of reproductive isolation, whereas a *recessive* mutant has a higher fixation probability otherwise. Delayed inheritance increases the fixation probability of a mutant if viability selection is weaker than reproductive isolation. Our results clarify the conflicting effects of viability selection and positive frequency-dependent selection due to reproductive isolation and provide a new perspective to single-gene speciation theory.

INTRODUCTION

Ever since Darwin, understanding the genetic and ecological conditions under which speciation occurs has been an ongoing challenge in evolutionary biology (Coyne and Orr 2004). One longstanding issue of debate in speciation theory concerns the number of genes that are necessary for speciation to occur. Under the classic Bateson-Dobzhansky-Muller (BDM) model, speciation requires changes in at least two genes because if there is one new allele with strong effects on heterozygote viability or mating compatibility but without epistasis to other genes, then the fitness of variants that harbor that allele should decrease, making the fixation of this allele in the population difficult. In contrast, negative epistatic interactions between independently derived alleles (A and B) at two loci can establish reproductive isolation between descendant genotypes (AAbb and aaBB) without reproductive isolation between the ancestral genotype (aabb) and daughter lineages (Bateson 1909; Dobzhansky 1936; Muller 1942).

Although the classical BDM incompatibility model has been influential in explaining the speciation process (Orr 1996; Gavrilets 2004; Bank et al. 2012), the model cannot explain the evolution of reproductive isolation via a single gene. Speciation that results from genetic substitution at a single locus is known as ‘single-gene speciation’ (Orr 1991).

57 Single-gene speciation has been of special interest for the following reasons: (1) “one-locus
58 models are a natural starting point for theoretical approaches to many evolutionary
59 phenomena” (Gavrilets 2004); (2) there are several examples of empirical evidence for the
60 determination of mating traits by a single-locus (see Gavrilets 2004; Servedio et al. 2011 for
61 review); and (3) a single speciation gene that pleiotropically contributes to reproductive
62 isolation and divergent adaptation through a single trait ('automatic magic trait' according to
63 Servedio et al. 2011) or several traits (Slatkin 1982) has been thought to promote ecological
64 speciation (Rundle and Nosil 2005). Speciation becomes less probable if one locus is
65 responsible for ecological adaptation and another locus is responsible for reproductive
66 isolation because recombination breaks down the association between the two loci
67 (Felsenstein 1981). Here, we refer to this dual function of a single gene as pleiotropic effects
68 or simply pleiotropy (Slatkin 1982). In spite of these longstanding interests and an increasing
69 number of studies that suggests the involvement of adaptation in speciation (Schluter 2009),
70 the theoretical framework to explain the process of single-gene speciation is not robust
71 because previous studies have relied heavily on numerical simulations (Kirkpatrick and
72 Ravigné 2002; Gavrilets 2004). In this paper, we use new analytical results to investigate the
73 effects of pleiotropy, allele dominance, population size, and maternal effect on the fixation

74 process of the speciation gene in single-gene speciation.

75 An excellent example of single-gene speciation is found in land snails (see
76 Schilthuizen and Davison 2005; Okumura et al. 2008 for review). Handedness is shown to be
77 controlled by two alleles at a single nuclear locus in phylogenetically segregated families of
78 pulmonate snails (Boycott et al. 1930; Degner 1952; Murray and Clarke 1976; Freeman and
79 Lundelius 1982; Ueshima and Asami 2003), and mating between opposite coiling individuals
80 rarely occurs (Johnson 1982; Gittenberger 1988; Asami et al. 1998). Thus, the handedness
81 gene is responsible for pre-mating isolation. Despite the positive frequency-dependent
82 selection against rare mutants predicted by the BDM model (Johnson 1982; Asami et al.
83 1998), it has been shown that evolutionary transitions from an abundant dextral (clockwise
84 coiling) species to a mutant sinistral (counter-clockwise coiling) species have occurred
85 multiple times (Ueshima and Asami 2003; Davison et al. 2005; Hoso et al. 2010; Gittenberger
86 et al. 2012).

87 Why is single-gene speciation possible in snails? Following Gittenberger (1988),
88 Orr (1991) proposed that small population sizes and maternal effect (i.e., delayed inheritance:
89 Fig. 1) in snail populations could promote single-gene speciation. Because snails have low
90 mobility, local populations tend to be isolated from one another, which causes repeated

91 extinction and colonization events. Consequently, the effective population sizes of snails are
92 small and genetic drift is strong (Arnaud and Laval 2004; Hoso 2012). Delayed inheritance of
93 handedness is a type of maternal effect in which an individual's phenotype is determined by
94 the genotype of its mother (Fig. 1: Boycott et al. 1930; Degner 1952; Murray and Clarke
95 1976; Freeman and Lundelius 1982). Subsequent theoretical studies on the evolution of snail
96 coiling have basically attributed the cause of single-gene speciation to these two factors (van
97 Batenburg and Gittenberger 1996; Stone and Björklund 2002; but see Davison et al. 2005).

98 In a recent study (Hoso et al. 2010), a 'right-handed predator' hypothesis was
99 proposed to explain the effects of pleiotropy on the single-gene speciation of snails. The
100 authors concluded that a gene controlling coiling direction of snails could pleiotropically
101 affects interchiral mating difficulty and anti-predator adaptation because of the 'handedness'
102 of the predator. Because most snails are dextral ('right-handed') (Vermeij 1975), predators
103 tend to be 'right-handed' (have evolved to specialize in the abundant dextral type of snail).
104 Such predators include box crabs (Shoup 1968; Ng and Tan 1985; Dietl and Hendricks 2006),
105 water-scavenger beetle larvae (Inoda et al. 2003), and snail-eating snakes (Hoso et al. 2007;
106 Hoso et al. 2010). Behavioral experiments revealed that right-handed predators tend to fail in
107 attempts to eat sinistral snails because of the left-right asymmetry of their feeding apparatuses

and behaviors (Inoda et al. 2003; Dietl and Hendricks 2006; Hoso et al. 2007). Therefore, although a mating disadvantage still exists, sinistral snails will have a survival advantage under right-handed predation. This can potentially promote the fixation of a sinistral allele, and indeed Hoso et al. (2010) found a positive correlation between the distribution of a right-handed predator (snake) and proportion of sinistral lineages in Southeast Asia. Although Hoso et al. (2010) showed a correlation *pattern*, the fixation *process* of the mutant allele in the speciation gene with pleiotropic effects underlying such pattern has not been fully investigated.

Here, we theoretically investigate the fixation process of a mutant allele in the speciation gene in single-gene speciation with and without pleiotropic effects. We seek to answer the following questions. (1) How do allele dominance, population size, and delayed inheritance affect single-gene speciation? What kind of mutant allele dominance (e.g., dominant, recessive, or subdominant) has the highest fixation probability? How do population size and delayed inheritance affect this tendency? (2) How does pleiotropy affect the process of single-gene speciation? On the one hand, when the mutant frequency is low, it would be better for heterozygotes to have the resident phenotype to mate with common resident genotypes because of positive frequency-dependent selection. On the other hand, the mutant

phenotype is advantageous under strong viability selection. Because of the conflicting factors acting on heterozygotes, the overall effects of allele dominance and delayed inheritance can be changed by the relative strengths of the pleiotropic effects of the speciation gene.

MODEL

To examine the questions of single-gene speciation described above, we consider a general allopatric speciation model. When a panmictic population splits into two geographically divided subpopulations, it is sufficient to compare fixation probabilities of a mutant allele in a single subpopulation to understand the likelihood of speciation (Orr 1991). We construct Wright-Fisher models of haploid or diploid individuals without delayed inheritance and diploid individuals with delayed inheritance to study the mutant allele frequency change through generations with reproductive isolation and viability selection.

We assume that mating partners are randomly chosen from the population and that mating between different phenotypes fails with probability r (Table 1) because of either pre- or post-zygotic factors (Slatkin 1982). A common phenotype enjoys an advantage over a rare one because a randomly chosen mate is more likely to be compatible (i.e., the same phenotype). This leads to positive frequency-dependent selection (favoring the more common

phenotype) in the mating character.

Haploid model

We first consider the simplest case of haploid inheritance. We denote the frequency of the mutant allele (A) by p and that of the wild type allele (a) by $1 - p$. The frequency after mating, $\tilde{p}$, is

$$\tilde{p} = \frac{p^2 + (1-r)p(1-p)}{1-2rp(1-p)}, \tag{1}$$

where r measures the intensity of reproductive isolation between the mutant and wild type ($0 \leq r \leq 1$, Table 1). Reproductive isolation is complete if $r = 1$, the mating is random if $r = 0$, and reproductive isolation is partial if $0 < r < 1$. The mutant frequency after one generation, p', is given by

$$p' = \frac{(1+s)\tilde{p}}{(1+s)\tilde{p} + 1\cdot(1-\tilde{p})}, \tag{2}$$

where s is a positive viability selection coefficient for a mutant (i.e., a mutant has higher

survivorship than a wild type). For example, if a mutant snail is sinistral, s represents the relative survival advantage of sinistral snails because of the right-handed predation by snakes (Hoso et al. 2010).

Diploid model without delayed inheritance

For the diploid model without delayed inheritance, a mutant arises as a single heterozygote (Aa) in a population of the wild type homozygotes (aa). We denote the degree of dominance of allele A by h such that $h = 0$ and $h = 1$ correspond to completely recessive and dominant mutant alleles, respectively. Under partial dominance ($0 < h < 1$), we consider two models. First, a three-phenotype model in which heterozygotes have an intermediate phenotype of the homozygous phenotypes, and the intensities of reproductive isolation and viability selection are determined by the degree of dominance (h), although this does not apply to snails (Table 1). Second, a two-phenotype (A and a) model in which a heterozygote has phenotypes A and a with probabilities h and $1 - h$, respectively (Appendix S8). We adopt the former model in the main text, but both models give qualitatively similar results (see Discussion). The frequencies of genotypes AA ($= x$) and Aa ($= y$) after mating, $\tilde{x}$ and $\tilde{y}$, are given by

$$T\tilde{x} = x^2 + \left[1-(1-h)r\right]xy + \frac{y^2}{4},$$
$$T\tilde{y} = \left[1-(1-h)r\right]xy + 2(1-r)xz + \frac{y^2}{2} + (1-hr)yz, \quad (3)$$

where $T = 1 - 2r\left[(1-h)xy + xz + hyz\right]$ and z (= 1 − x − y) represents the frequency of the resident allele homozygote, aa (Table 1). The frequencies in the next generation, x' and y', are

$$x' = \frac{(1+s)\tilde{x}}{(1+s)\tilde{x} + (1+hs)\tilde{y} + 1\cdot\tilde{z}},$$
$$y' = \frac{(1+hs)\tilde{y}}{(1+s)\tilde{x} + (1+hs)\tilde{y} + 1\cdot\tilde{z}}, \quad (4)$$

where s is the selective advantage of the mutant phenotype in terms of viability. By definition, $\tilde{z} = 1 - \tilde{x} - \tilde{y}$.

The condition for the invasion of the mutant allele in a population of infinite size is analyzed by examining the local stability of equilibrium without the mutant (x = y = 0) in equation (4). The fixation probability of a mutant for the case with random genetic drift because of a finite population size is examined in three ways. First, assuming r and s values

are small, a two-dimensional representation of genotype dynamics (4) can be approximated with one-dimensional dynamics along Hardy-Weinberg equilibrium (Fig. 2). Then applying the diffusion approximation (Crow and Kimura 1970) leads to an analytical formula for the fixation probability with an arbitrary degree of dominance for the mutant allele. Second, for a very small population, because the diffusion approximation is not applicable, the exact fixation probability is numerically calculated with a Markov chain approach (first-step analysis, Pinsky and Karlin 2010). Third, the fixation probability is estimated from extensive Monte Carlo simulations of full dynamics (4) under random genetic drift. We assume symmetric mutation rates for the dominant and recessive alleles and compare their fixation probabilities to predict the allele dominance of sinistral alleles in snails.

Diploid model with delayed inheritance

With delayed inheritance, the phenotype of an individual is determined by its mother's genotype. In this model, 6 pairs of genotype-phenotype combination are possible; however, with complete recessiveness or dominance, only 5 pairs can be realized. Here, we assume that the mutant allele A is completely dominant. The counterpart case for a completely recessive mutant can be analyzed in a parallel manner (see Appendix S2). With three

genotypes (AA, Aa, and aa) and two phenotypes (A and a), the six genotype-phenotype combinations are denoted as AA_A, AA_a, Aa_A, Aa_a, aa_A, and aa_a. For example, Aa_A represents an individual with genotype Aa and phenotype A. Because allele A is dominant, AA_a is simply impossible in the genetic system of delayed inheritance (Table S1).

We assume that the mutation in the speciation gene occurs in the embryo. In the genetic system of delayed inheritance, the first mutant's phenotype is the same as its wild type mother. We denote the frequencies of each combination of genotypes and phenotypes, AA_A, Aa_A, Aa_a, aa_A, and aa_a by x_A, y_A, y_a, z_A, and z_a (= $1 - x_A - y_a - z_A - z_a$), respectively. Let p (= $x_A + (y_A + y_a)/2$) and q (= $1 - p = (y_A + y_a)/2 + z_A + z_a$) be the frequencies of dominant (A) and recessive (a) alleles. The frequencies after mating are

$$
\begin{aligned}
T\tilde{x}_A &= p^2 - ry_a\left(x_A + \frac{y_A}{2}\right),\\
T\tilde{y}_A &= p(1-x_A) - r\left[z_a\left(x_A + \frac{y_A}{2}\right) + y_a\left(x_A + y_A + \frac{z_A}{2}\right)\right],\\
T\tilde{y}_a &= p(1+x_A-2p) - r\left[z_a\left(x_A + \frac{y_A}{2}\right) + \frac{y_a z_A}{2}\right],\\
T\tilde{z}_A &= (p-x_A)(1-p) - \frac{r}{2}\left[y_A(y_a+z_a) + y_a z_A\right],
\end{aligned}
\tag{5}
$$

where $T = 1 - 2r(x_A + y_A + z_A)(y_a + z_a)$. Because phenotype A is favored under viability selection, the frequencies after viability selection are given by

$$x'_{\mathrm{A}} = \frac{(1+s)\tilde{x}_{\mathrm{A}}}{W}, y'_{\mathrm{A}} = \frac{(1+s)\tilde{y}_{\mathrm{A}}}{W}, y'_{\mathrm{a}} = \frac{\tilde{y}_{\mathrm{a}}}{W}, z'_{\mathrm{A}} = \frac{(1+s)\tilde{z}_{\mathrm{A}}}{W}, z'_{\mathrm{a}} = \frac{\tilde{z}_{\mathrm{a}}}{W}, \tag{6}$$

where $W = 1 + s(\tilde{x}_{\mathrm{A}} + \tilde{y}_{\mathrm{A}} + \tilde{z}_{\mathrm{A}})$ is the mean fitness of the population. See Appendix S2 for the case of a recessive mutant allele.

Similar to the without-delayed-inheritance model, the condition in which the mutant invades a population of infinite size is analyzed by examining the local stability of mutant-free equilibrium, $x_A = y_A = y_a = z_A = 0$, with 4-dimensional genotype dynamics (5)-(6). For the fixation probability of the mutant in a finite population, genotype dynamics are reduced to a single dimension by assuming small *r* and *s*, through Hardy-Weinberg and quasi-equilibrium of genotype-phenotype combination frequencies with the maternal inheritance dynamics, which also leads to an analytical formulation. The first-step analysis for a very small population and the Monte Carlo simulations are performed in the same manner as in the case without delayed inheritance.

First-step analysis can also be applied to large populations, but the calculation is formidable when *N* is large (especially for the diploid model with delayed inheritance that has four variables). Therefore, we present results for the *N* = 3 condition and compare these

results to the $N = 10$, $N = 1{,}000$ (Monte Carlo simulations), and $N \to \infty$ (diffusion approximation) conditions.

RESULTS

Through a deterministic analysis of infinite populations, we confirm that if the degree of reproductive isolation between mating phenotypes is larger than the coefficient of viability selection ($r > s$), the system shows bistability: the monomorphism of either allele (A or a) is stably maintained under positive frequency-dependent selection due to reproductive isolation for haploid and diploid conditions as well as delayed and non-delayed inheritance conditions. A rare mutant allele cannot invade infinite populations as predicted by the classic theory (Bateson 1909; Dobzhansky 1936; Muller 1942). Thus, genetic drift in finite populations is a prerequisite for single-gene speciation with weak viability selection ($r > s$) (Gavrilets 2004).

Invasion conditions in deterministic models

We demonstrate that pleiotropic effects can promote single-gene speciation, as proposed by Hoso et al. (2010). Because a single speciation gene causes positive

257 frequency-dependent selection, viability selection must be strong enough for the mutant allele

258 to successfully invade a population (Fig. 3). The required selection coefficient for a mutant

259 allele to invade is $s > r/(1-r)$ in haploid and diploid models with complete dominance (i.e.,

260 the mutant is either completely dominant or recessive) and $s > r/(1-hr)$ for the diploid

261 model with partial dominance (Appendix S1, S2, and S8). In the haploid model, equations (1)

262 and (2) are approximated as $p' \approx (1+s)(1-r)p$ if the mutant frequency is small ($p \approx 0$).

263 When $(1 + s)(1 - r) < 1$, the system is bistable and positive frequency-dependent selection

264 excludes rare alleles. There are two locally stable equilibria at $p = 0$ and $p = 1$, and a locally

265 unstable equilibrium, $p_c = [r(1+s)-s]/[r(2+s)]$, that divides two basins of attraction. As

266 the mutant allele becomes more selectively favored (s (> 0) is increased), the unstable

267 equilibrium moves closer to zero and eventually disappears once s is large enough to satisfy

268 $(1 + s)(1 - r) = 1$. When $(1 + s)(1 - r) > 1$ or $s > r/(1 - r)$, there is a globally stable equilibrium

269 at $p = 1$ and the mutant allele increases and eventually fixes irrespective of its initial

270 frequency (Fig. 3). Note that invasion is impossible when reproductive isolation is complete

271 ($r = 1$), and this again suggests the importance of genetic drift in small populations.

272 For the diploid model, partial dominance makes single-gene speciation more

273 feasible because heterozygotes can simultaneously maintain their mating probability and

survival advantage. We derive the condition for the mutant allele to be able to invade the wild type population as $s > r/(1 - hr)$ when $h \neq 0$ by analyzing recursion equations (3) and (4) (Appendix S1). Interestingly, the invasion condition of the complete recessive ($h = 0$) allele ($s > r/(1 - r)$) differs from $s > r$, that is the limit of $h \rightarrow 0$ for the invasion condition of the partially dominant mutant (Appendix S1) because with small h in the partial dominance model, there is a stable internal (coexisting) equilibrium, which does not exist for complete recessiveness (Fig. S4). Heterozygotes with a completely recessive mutant allele are neutral for viability selection, but the invasion condition is equivalent to the completely dominant ($h = 1$) allele (Fig. 3). In addition, because of a locally stable equilibrium in which the mutant allele coexists with the resident allele if r is large and h is small (Fig. S4), the invasibility of a mutant (Fig. 3) does not necessarily imply its fixation in the population. For the diploid model with delayed inheritance, the invasion condition in infinite populations is $(1 + s)(1 - r) > 1$ (Appendix S2), which is identical to the haploid and diploid models without delayed inheritance (Fig. 3). However, the largest eigenvalue of the Jacobian matrix in the linearized system is smaller than the dominant allele in the diploid model without delayed inheritance (Appendix S2), which corresponds to the fact that delayed inheritance makes the invasion of a mutant more feasible in a finite population, which we discuss later. Note that under positive

frequency-dependent selection, viability selection does not need to be constantly strong. Once the mutant allele frequency exceeds the unstable equilibrium, the mutant phenotype becomes advantageous in mating and strong viability selection is no longer necessary.

Fixation in a finite population with haploid inheritance

The change in allele frequency after one generation, $\Delta p = p' - p$, in the haploid model is

$$\Delta p = \frac{p(1-p)\left[r(2p-1)+s-sr(1-p)\right]}{(1+s\tilde{p})\left[1-2rp(1-p)\right]}, \tag{7}$$

which is derived from equations (1) and (2). Assuming r and s are small, we can consider a continuous time model for the change in allele frequency. Neglecting higher order terms for r and s, we have the deterministic dynamics,

$$\dot{p} = p(1-p)\left[r(2p-1)+s\right]. \tag{8}$$

Equation (8) has two stable equilibria at $p = 0$ and $p = 1$, and an internal unstable equilibrium

at $p = p_c = (1 - s/r)/2$ when $r > s$. However, if $s \geq r$, only $p = 1$ is locally stable. When $s = 0$, the unstable equilibrium is at $p = 1/2$ and the derivative of allele frequency dynamics is negative when p is smaller than 1/2 and positive when p is larger than 1/2 (solid gray line in Fig. 4A). This result for the haploid model serves as the baseline when we discuss the effects of dominance and delayed inheritance.

If the population is finite, a single mutant can go to fixation and replace the wild type even when $r > s$. Assuming r and s are small and the population size (N) is large, we obtain the fixation probability of a single mutant by applying the diffusion approximation as

$$\rho = u(1/N) = \frac{1/N}{\int_0^1 \exp\left[\frac{R}{2}\left(p - p^2\right) - \frac{S}{2}p\right]dp}, \tag{9}$$

where $R = 4Nr$ and $S = 4Ns$. If and only if the locally unstable equilibrium is less than 1/3, $p_c = (1 - S/R)/2 < 1/3$, there exists some N with which the fixation probability ρ is higher than that of a neutral mutant ($1/N$) (one-third law, Nowak et al. 2004).

Fixation in a finite population with diploid inheritance

The one-dimensional diffusion process along the curve of Hardy-Weinberg equilibrium

The dynamics of dominant and recessive alleles in the diploid models are also subject to positive frequency-dependent selection, but variation in the position of the internal equilibrium and selection gradient along the mutant allele frequency depends heavily on which allele is dominant, which has a large effect on the process of fixation. Namely, a dominant allele is favored over a recessive allele at intermediate frequencies; whereas, a recessive allele is favored when it is at either low or high frequencies (compare red and blue dashed curves in Fig. 4D). To show this and to evaluate the fixation probability of a mutant later, we approximate the two-dimensional genotype frequency dynamics of the diploid model to one-dimensional allele frequency dynamics. Genotype frequency dynamics are not strictly at Hardy-Weinberg (HW) equilibrium, and this deviation is caused by reproductive isolation and viability selection (Fig. 2). However, we show that if both r and s are small, frequency dynamics first approach HW equilibrium and slowly converge to a locally stable equilibrium at $p = 0$ or 1 (Crow and Kimura 1970 demonstrated this without viability selection). Assuming that r and s are in the order of ε, which is a small positive constant, we expand the dynamics of equations (3) and (4) in Taylor series with respect to ε. The leading order dynamics for the zygote frequencies becomes

$$x' = p^2 + O(\varepsilon),$$
$$y' = 2p(1-p) + O(\varepsilon). \tag{10}$$

Thus, up to the leading order, genotype frequencies are in HW equilibrium. From this, it follows that the allele frequencies do not change with time ($p' = p$) up to the leading order. By assuming a large population size, small values of r and s, and HW equilibrium (10), we can approximate the deterministic allele frequency dynamics by

$$\dot{p} = p(1-p)\left\{r\left[p(2p^2-1) - h(6p^2-6p+1)\right] + s\left[p + h(1-2p)\right]\right\}. \tag{11}$$

The scaled derivatives of the frequency dynamics when h = 0, 1/2, and 1 without viability selection (s = 0) are shown by dotted lines (Figs. 4 and S1).

Effect of dominance on the fixation probability of a mutant in a large finite population

Despite the large difference in the frequency-dependent fitness profiles between dominant and recessive alleles (Fig 4D), both alleles have the same fixation probability if there is no viability selection in large populations (Fig. 5H). From the allele frequency

dynamics (11) under Hardy-Weinberg equilibrium that is approximately followed throughout the process for small r and s, we obtain the fixation probability of a single mutant allele, $\rho_h = u(1/(2N))$, with the diffusion approximation (Appendix S3) where $u(p)$ is the fixation probability of a mutant with the initial frequency p. The fixation probability of a single mutant ρ_h for a given degree h of dominance is given by

$$\rho_h = \frac{1/(2N)}{\int_0^1 \exp\left\{ Ry(1-y)\left[\frac{y}{2}(1+y) - h(2y-1)\right] - Sy\left[\frac{y}{2} + h(1-y)\right]\right\} dy}, \tag{12}$$

where $R = 4Nr$ and $S = 4Ns$, as defined before. Thus, the recessive ($h = 0$) and dominant ($h = 1$) mutants have exactly the same fixation probability if there is no viability selection ($s = 0$),

$$\rho_0 = \frac{1/(2N)}{\int_0^1 \exp\left[\frac{R}{2}(1-y)y^2(1+y)\right] dy} = \frac{1/(2N)}{\int_0^1 \exp\left[\frac{R}{2}y(1-y)^2(2-y)\right] dy} = \rho_1, \tag{13}$$

which can be shown by changing the variables in the integral (Appendix S3).

Very small populations

When population size is very small and viability selection is absent, the recessive mutant allele has a higher fixation probability than the dominant allele. We show this result with Monte Carlo simulations (Fig. 5E) and numerical calculations of exact fixation probabilities using first-step analysis (Fig. 5B, Appendix S5, S6). The discrepancy between the cases of large (diffusion approximation results) and small population sizes could be because of the different contributions of absolute numbers of individuals to the frequency dynamics. Although we assume that a mutant first arises as a single heterozygous individual in the diploid model, the initial mutant frequency is higher in a small population. Thus, the first heterozygous individual with a dominant mutant allele is more strongly selected against than a recessive mutant allele in small populations (Fig. 4D).

Effect of delayed inheritance

As shown in equations (14) and (15) below, delayed inheritance halves the strength of positive frequency-dependent selection (Fig. 4), which increases the fixation probability of a mutant in large populations (Fig. 5I). Assuming HW equilibrium when r and s are small (Appendix S4), the approximated frequency dynamics of the dominant mutant allele in the diploid model with delayed inheritance is given by

$$\dot{p} = \frac{1}{2} p(1-p)^2 \left[-r(2p^2 - 4p + 1) + s \right]. \tag{14}$$

Furthermore, the frequency dynamics of the recessive mutant allele is

$$\dot{p} = \frac{1}{2} p^2 (1-p) \left[r(2p^2 - 1) + s \right]. \tag{15}$$

Comparing these equations to equation (11) with $h = 1$ and $h = 0$, we find that the right-hand side of equations (14) and (15) are exactly one-half of the right-hand side of equation (11) with $h = 1$ and $h = 0$, respectively (solid lines in Fig. 4). Therefore, regardless of whether the mutant allele is dominant or recessive, the fixation probabilities for a mutant are higher when delayed inheritance is present than when delayed inheritance is absent (Fig. 5I, Appendix S4). The fact that the magnitudes of r and s relative to the strength of genetic drift $1/N$ are halved may be reinterpreted to mean that delayed inheritance effectively halves the effective population size. This is probably because the phenotype is determined only by the mother's genotype with no contribution from the father. The tendency for the model with delayed inheritance to have higher fixation probabilities remains the same in small populations where

diffusion approximation cannot apply (Figs. 5C, 5F, Appendix S7). With delayed inheritance, fixation probabilities can be increasing functions of reproductive isolation (r) when viability selection is strong ($s >> 1$) and the population size is very small ($N = 3$), which contrasts the general tendency (i.e., for fixation probabilities to be decreasing functions of reproductive isolation) (Fig. S6).

Effect of reproductive isolation and viability selection

Positive frequency-dependent selection and viability selection work on the mutant phenotype; therefore, individuals with the mutant phenotype get conflicting effects from the two selection pressures when the mutant allele frequency is low. When reproductive isolation is relatively weak, the survival advantage of the mutant phenotype exceeds its mating disadvantage; on the other hand, with relatively strong reproductive isolation, the survival advantage of the mutant phenotype cannot compensate for its mating disadvantage when the mutant is rare. In large populations, the dominant and recessive mutant alleles have the same fixation probability without pleiotropy (when $s = 0$: Fig. 5), whereas the dominant mutant allele has higher fixation probability when $r = 0$ (Haldane's sieve: see Discussion). Thus fixation probabilities of the dominant mutant allele are always higher than those of the

recessive allele. Delayed inheritance halves selection pressures (equations 14 and 15); this is advantageous when positive frequency-dependent selection due to reproductive isolation is strong (Fig. 4), but is not advantageous when viability selection is strong. Therefore, the dominant mutant allele without delayed inheritance has the highest fixation probability when reproductive isolation (*Nr*) is weak and viability selection (*Ns*) is strong, whereas the dominant mutant allele with delayed inheritance has the highest fixation probability when reproductive isolation is strong and viability selection is weak in large populations (Fig. 6C). In small populations, the recessive mutant allele with delayed inheritance has the highest fixation probability when reproductive isolation is strong and viability selection is weak (Figs. 6A, 6B). Therefore, the more frequently fixed allele can be dominant when viability selection is relatively strong (Fig. 6), which is in contrast to speciation without pleiotropy.

DISCUSSION

In finite populations without pleiotropy, dominant and recessive alleles have the same fixation probability in large populations; however, a recessive allele has a higher fixation probability in very small populations. The effects of population size are contrasting, but most left-right reversals are likely to have occurred in small isolated populations (Orr

1991; Hoso 2012). Therefore, the recessive mutant allele will fix more frequently than the dominant allele in the absence of right-handed predation, if the dominant and recessive mutations arise in the same probability.

There are conflicting arguments about allele dominance; Orr (1991) wrote "the probability of fixation of a maternal mutation is roughly independent of its dominance" in dioecious populations, whereas hermaphroditic populations with selfing "…*decrease* the chance that a dominant mutation will be fixed." In contrast, van Batenburg and Gittenberger (1996) showed that the dominant mutant allele has a higher fixation probability. We point out that this discrepancy is mainly because of different assumptions of the initial numbers of the mutant allele. Both Orr (1991) and we computed the fixation probability of a single mutant, whereas van Batenburg and Gittenberger (1996) even considered 16 invaders with the total population size 32, assuming mass invasion from neighboring sinistral populations. By accounting for the assumptions of each argument, the conflicting results can be explained because the recessive mutant allele has a higher fitness when it is rare, whereas the dominant mutant allele has a higher derivative when the frequency is intermediate (Fig. 4D). We changed the initial numbers of mutants in Monte Carlo simulations and obtained results to support this claim (data not shown). The fixation probability is usually calculated for a single

459 *de novo* mutation. Thus, as long as the initial mutant is a single heterozygote, we analytically
460 and numerically showed that the recessive mutant allele has a higher fixation probability in
461 small populations and both alleles have the same probability in large populations (Fig. 5).

462 The effect of reproductive isolation and viability selection (Fig. 6) is consistent with
463 "Haldane's sieve", where there is a bias against the establishment of recessive adaptive alleles
464 (Haldane 1924, 1927; Turner 1981). Previous studies revealed that certain factors, including
465 self-fertilization (Charlesworth 1992), adaptation from standing genetic variation (Orr and
466 Betancourt 2001), and spatial structure (Whitlock 2003), can change the fixation bias of allele
467 dominance. Our results showed that the adaptive mutation that pleiotropically contributes to
468 reproductive isolation can also change this bias.

469 We consider two cases of partial dominance (h = 0.5) in the diploid model without
470 delayed inheritance. Although these do not apply to snails, the results would be important for
471 understanding general single-gene speciation processes. Because of different fitness gradients
472 along allele frequencies (Fig. S1), the three-phenotype model has a higher fixation probability
473 than the two-phenotype model, which has similar results as the haploid model (Figs. 5B, 5E,
474 5H, S2, and S3). With pleiotropy, the fixation probability in the three-phenotype model is the
475 highest when reproductive isolation is strong and viability selection is weak in large

476 populations (Fig. S5C), while it is the highest in intermediate intensity of reproductive
477 isolation and viability selection in small populations (Figs. S5A and S5B).

478 In single-gene speciation in snails, the intensity of interchiral mating difficulty, r,
479 should be an important parameter; interchiral mating is almost impossible in flat-shelled
480 snails that perform two-way face-to-face copulation (large r), whereas it is relatively easy for
481 tall-shelled snails that can copulate by shell mounting (small r) (Asami et al. 1998). Therefore,
482 even with the same population size and right-handed predation pressure, the frequently fixed
483 allele dominance can be changed (Fig. 6A). When right-handed predation is weak or absent
484 and interchiral mating is difficult (flat-shelled snails), the frequently fixed allele should be
485 recessive. On the other hand, the frequently fixed allele can be dominant when right-handed
486 predation is strong and interchiral mating is easy (tall-shelled snails).

487 We have calculated fixation probabilities for various values of N, r, s, and the
488 dominance of the mutant allele. Phylogenetic information (Ueshima and Asami 2003; Hoso et
489 al. 2010) can be used to infer these parameters because the number of left-right reversals in
490 the phylogeny is influenced by fixation probabilities. Let P_S be the duration that the snail
491 phenotype remains sinistral, and P_D be the duration for dextrality. The expected sojourn time
492 in the sinistral phenotype is $P_S = 1/(N\mu\rho_D)$, where μ is the mutation rate of the speciation gene

493 changing to the dextral allele and ρ_D is the fixation probability of the mutant dextral allele.

494 Assuming that the mutation is symmetrical and population size is constant, the ratio of these

495 values is given by $P_S/P_D = (N\mu\rho_D)/(N\mu\rho_S) = \rho_D/\rho_S$. If left-right reversals have occurred

496 frequently, the ratio estimated from the phylogeny data should approach the theoretical

497 prediction. The extent of assortative mating, *r*, (Asami et al. 1998) and biased predation

498 pressure by right-handed predators, *s*, (Hoso et al. 2007; Hoso et al. 2010) are known from

499 experiments. Thus, it would be possible to estimate the population size and allele dominance

500 by statistical inference. However, in addition to the somewhat arbitrary assumptions of

501 constant population size, symmetrical mutation, and equilibrium states, reconstruction of

502 ancestral states is generally challenging when the trait evolves adaptively (Cunningham 1999).

503 Furthermore, we did not consider gene flow between spatially neighboring dextral and

504 sinistral populations (Davison et al. 2005) or internal selection against left-right reversal

505 (Utsuno et al. 2011). Thus, we propose these estimations as a future research subject.

506 In conclusion, although the conventional theory by Bateson, Dobzhansky and

507 Muller is still valid, our study has shown that single-gene speciation is likely to be more

508 realizable than previous studies have assumed by combining various factors including

509 recessiveness, delayed inheritance, small population size, and pleiotropic effects that increase

510 mutant viability. Specifically, delayed inheritance and pleiotropic effects of the speciation
511 gene (e.g., right-handed predation on snails) can promote single-gene speciation, which
512 supports the hypothesis that right-handed predation by specialist snakes is responsible for
513 frequent left-right reversals of land snails in Southeast Asia (Hoso et al. 2010). Sinistral
514 species have frequently evolved outside the snake range without right-handed predation, and
515 in this case, our study suggests that allele dominance is important as well as small population
516 size and delayed inheritance (Orr 1991). Interestingly, population size and pleiotropy can
517 change the effects of allele dominance and delayed inheritance on speciation. Ueshima and
518 Asami (2003) constructed a molecular phylogeny and speculated that the dextral allele
519 appears to be dominant for *Euhadra* snails based on the breeding experiments with a
520 *Bradybaena* species, citing van Batenburg and Gittenberger (1996); however, caution is
521 needed because reversal could occur by a *de novo* mutation and viability selection by
522 right-handed predators might be involved in speciation (Hoso et al. 2010). Recent
523 technological developments in molecular biology make it possible to investigate the
524 dominance of alleles in ecologically important traits as well as their ecological and
525 evolutionary effects (e.g., Rosenblum et al. 2010). Although the search for a coiling gene (the
526 speciation gene) in snails is still underway (e.g., Grande and Patel 2009; Kuroda et al. 2009),

our prediction—that the recessive allele has a higher fixation probability in the absence of specialist predators ($s = 0$) for flat-shelled snails (large r), whereas the dominant allele can have a higher fixation probability in the presence of specialist predators ($s > 0$) for tall-shelled snails (small r) —will be testable. This hypothesis could be tested, for example, by analyzing the correlations between the presence of right-handed predators and sinistral allele dominance.

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TABLES

Table 1. The diploid model without delayed inheritance ($h = 0$: a is a dominant allele, $h = 1$: A is a dominant allele)

Mating comb.	Mating prob.	AA	Aa	aa
AA × AA	x^2	1	0	0
AA × Aa	$2[1 - (1 - h)r]xy$	1/2	1/2	0
AA × aa	$2(1 - r)xz$	0	1	0
Aa × Aa	y^2	1/4	1/2	1/4
Aa × aa	$2(1 - hr)yz$	0	1/2	1/2
aa × aa	z^2	0	0	1

FIGURE LEGENDS

Figure 1. Chirality inheritance determined by maternal effects of dominant dextral (D) and recessive sinistral (s) alleles at a single nuclear locus (delayed inheritance). Black and gray spirals indicate dextral and sinistral phenotypes, respectively. In the second generation, individuals of the same genotype (Ds) develop into the opposite enantiomorph depending on the maternal genotype (DD or ss). Note that snails are androgynous.

Figure 2. Representative example for the trajectory of the fixation process of a mutant allele that starts as a single heterozygote (black line) in the diploid model without delayed inheritance. *X*-axis: frequency of the resident allele homozygotes, aa (z). *Y*-axis: frequency of the mutant allele homozygotes, AA (x). Note that $x + z \leq 1$ (dashed line). The initial condition is at $(z, x) = (1 - 1/N, 0)$ (black point). The gray curve ($x = 1 + z - 2\sqrt{z}$) indicates HW equilibrium. Parameter values are $N = 30$, $r = 0.1$, $s = 0.1$, and $h = 1$.

Figure 3. Deterministic invasion conditions for a mutant allele. Invasion is possible above each line. *X*-axis: reproductive isolation parameter (r). *Y*-axis: viability selection coefficient (s). Completely recessive and dominant mutant alleles ($h = 0$ and 1) require a large selection

coefficient for invasion, whereas partially dominant alleles (e.g., h = 0.5) require a smaller selection coefficient. Note that the invasion condition of the completely recessive mutant allele differs from the limit of $h \rightarrow 0$ (dotted line).

Figure 4. Allele frequency dynamics affected by positive frequency-dependent selection due to reproductive isolation (indicated by white arrows). Here is no viability selection (s = 0). X-axis: mutant allele frequency (p). Y-axis: scaled derivatives of the mutant allele ($\dot{p}/r$). A: The haploid model (solid gray line, eq. 8). An unstable equilibrium at p = 1/2 (white point) divides two basins of attraction. Stable equilibria are at p = 0 and 1 (black points). B: The diploid models with the dominant mutant allele without delayed inheritance (dotted red line, eq. 11 when h = 1) and with delayed inheritance (solid red line, eq. 14). An unstable equilibrium is at $p = 1-1/\sqrt{2}$. C: The diploid models with the recessive mutant allele without delayed inheritance (dotted blue line, eq. 11 when h = 0) and with delayed inheritance (solid blue line, eq. 15). An unstable equilibrium is at $p = 1/\sqrt{2}$. D: Comparison of the diploid models with the dominant (red) and recessive (blue) alleles. Intersection points are at $p = 1/2-\sqrt{3}/6$ and $1/2+\sqrt{3}/6$ (gray lines).

Figure 5. Relative fixation probabilities of a single mutant with reproductive isolation to that of a neutral mutant. Here is no viability selection ($s = 0$). A-F: X-axis is reproductive isolation parameter (r). G-I: X-axis is four times the product of reproductive isolation parameter and effective population size ($4Nr$). Y-axis is the product of fixation probability and effective population size ($N\rho$ in the haploid model and $2N\rho$ in the diploid models). A-C: $N = 3$ (first-step analyses and Monte Carlo simulations), D-F: $N = 10$ (Monte Carlo simulations), G-I: $N \rightarrow \infty$ (diffusion approximation) and $N = 1000$ (Monte Carlo simulations). A, D, G: Solid gray lines: the haploid model. B, C, E, F, H, I: Blue lines: the recessive mutant allele, red lines: the dominant mutant allele, green lines: the partial dominance model with two phenotypes ($h = 0.5$), solid lines: with delayed inheritance, dotted lines: without delayed inheritance. Points represent the results of Monte Carlo simulations. The solid gray line in Fig. 5G and the dotted green line in Fig. 5H are identical. The dotted blue and red lines (the diploid model without delayed inheritance) are overlapping in Fig. 5H. The solid blue and red lines (the diploid model with delayed inheritance) are overlapping in Fig. 5I.

Figure 6. The alleles with the highest fixation probabilities given certain strength of reproductive isolation and viability selection. Note that black lines do not represent invasion

714 conditions unlike Fig. 3. A: $N = 3$ (first-step analyses), B: $N = 10$ (Monte Carlo simulations),

715 C: $N \rightarrow \infty$ (diffusion approximation). A, B: *X*-axis is reproductive isolation parameter (r)

716 and *Y*-axis is viability selection coefficient (s). C: *X*-axis is four times the product of

717 reproductive isolation parameter and effective population size ($4Nr$) and *Y*-axis is four times

718 the product of viability selection coefficient and effective population size ($4Ns$). When $4Ns =$

719 0, both dominant and recessive mutant alleles with delayed inheritance have the same fixation

720 probability (dashed line). DI: delayed inheritance.

Online Supporting Information

Appendix S1: Invasion condition in the diploid model without delayed inheritance

We denote the frequencies of the genotypes, AA, Aa, and aa by x, y, and z (= $1 - x - y$). The frequencies after mating are

$$
\begin{aligned}
Tx' &= x^2 + \left[1-(1-h)r\right]xy + \frac{y^2}{4}, \\
Ty' &= \left[1-(1-h)r\right]xy + 2(1-r)xz + \frac{y^2}{2} + (1-hr)yz, \\
Tz' &= \frac{y^2}{4} + (1-hr)yz + z^2,
\end{aligned}
\tag{A1}
$$

where $T = 1 - 2r\left[(1-h)xy + xz + hyz\right]$ is the sum of the frequencies of three genotypes after mating (see Table 1 for the derivation). The frequencies in the next generation after viability selection favoring a mutant phenotype is

$$
\begin{aligned}
x' &= \frac{(1+s)x'}{(1+s)x' + (1+hs)y' + z'}, \\
y' &= \frac{(1+hs)y'}{(1+s)x' + (1+hs)y' + z'}, \\
z' &= \frac{z'}{(1+s)x' + (1+hs)y' + z'}.
\end{aligned}
\tag{A2}
$$

Here we assume that A is the mutant allele and a is the wild-type allele. When h = 1, the mutant allele is dominant; whereas, it is recessive when h = 0. We first consider the condition for the invasion of the completely or partially dominant mutant ($0 < h \le 1$). We then examine the invasibility condition for the completely recessive mutant ($h = 0$), in which we need to consult the center manifold theorem (Guckenheimer and Holmes 1983).

(i) Invasibility of the completely and partially dominant mutant ($0 < h \le 1$)

We linearize the dynamics (A2) for small x and y:

$$
\begin{pmatrix} x' \\ y' \end{pmatrix} = \begin{pmatrix} 0 & 0 \\ 2(1-r)(1+hs) & (1+hs)(1-hr) \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix}
\tag{A3}
$$

The largest eigenvalue of the linearized system is $(1+hs)(1-hr)$. Thus the mutant can invade if and only if $(1+hs)(1-hr) > 1$. This condition can be rewritten as $s > r/(1-hr)$.

(ii) Invasibility of the completely recessive mutant ($h = 0$)

If the mutant allele is completely recessive ($h=0$), the linearized system is also given by with $h=0$:

$$\begin{pmatrix} x' \\ y' \end{pmatrix} = A\begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} 0 & 0 \\ 2(1-r) & 1 \end{pmatrix}\begin{pmatrix} x \\ y \end{pmatrix}. \tag{A4}$$

As the largest eigenvalue is 1, we need to have higher order terms of x and y to examine the local stability of $x=y=0$. The Taylor expansion of (A2) up to the quadratic terms of x and y yields

$$\begin{pmatrix} x' \\ y' \end{pmatrix} = \begin{pmatrix} 0 & 0 \\ 2(1-r) & 1 \end{pmatrix}\begin{pmatrix} x \\ y \end{pmatrix} + \begin{pmatrix} f(x,y) \\ g(x,y) \end{pmatrix}, \tag{A5}$$

with

$$\begin{aligned} f(x,y) &= (1+s)\left[x^2 + (1-r)xy + \frac{y^2}{4}\right], \\ g(x,y) &= -2(1-r)(1-2r)x^2 - (2-3r)xy - \frac{y^2}{2}. \end{aligned} \tag{A6}$$

The linear part of (A5) can be diagonalized by the transformation

$$\begin{pmatrix} x \\ y \end{pmatrix} = P\begin{pmatrix} u \\ v \end{pmatrix}, \text{ with } P = \begin{pmatrix} 0 & -\dfrac{1}{2(1-r)} \\ 1 & 1 \end{pmatrix}, \tag{A7}$$

where the column vectors of P are the eigenvectors corresponding to the eigenvalues 1 and 0 of matrix A. This yields

$$\begin{aligned} \begin{pmatrix} u' \\ v' \end{pmatrix} &= \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix}\begin{pmatrix} u \\ v \end{pmatrix} + P^{-1}\begin{pmatrix} f(x,y) \\ g(x,y) \end{pmatrix} \\ &\equiv \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix}\begin{pmatrix} u \\ v \end{pmatrix} + \begin{pmatrix} F(u,v) \\ G(u,v) \end{pmatrix}, \end{aligned} \tag{A8}$$

with

$$\begin{aligned} F(u,v) &= -\frac{1}{2}(r-s+rs)u^2 - \frac{r}{2(1-r)}uv + \frac{(2-r)r(1+s)}{2(1-r)}v^2, \\ G(u,v) &= -\frac{1}{2}(1-r)(1+s)u^2 - \frac{(2-r)r(1+s)}{2(1-r)}v^2. \end{aligned} \tag{A9}$$

Define the center manifold $W^c = \{(u,v) \mid v = k(u), k'(0) = k''(0) = 0\}$ on which the trajectory

near $u = v = 0$ stays throughout the process. The simplest form would be $k(u) = au^2$. In order that the point (u', v') is also on the center manifold, we should have $v' = k(u')$. Substituting $u' = u + F(u, k(u))$ and $v' = G(u, k(u))$ into this yields

$$G(u, au^2) - a\left[u + F(u, au^2)\right]^2 = 0. \tag{A10}$$

Equating the coefficient of the leading term to zero, a is determined as

$$a = -\frac{1}{2}(1-r)(1+s). \tag{A11}$$

The slow dynamic of u restricted on the center manifold is then

$$u' = u + F(u, k(u)) = u - \frac{1}{2}(r - s + rs)u^2, \tag{A12}$$

and hence u converges to zero if $r - s + rs > 0$, or the mutant can invade if $r - s + rs < 0$ (or $(1-r)(1+s) > 1$). This invasibility condition for the completely recessive mutant is equivalent to that for the completely dominant mutant, but, interestingly, differs from the condition $s > r$ in the limit of $h \to 0$ for the invasibility condition of the partially dominant mutant.

Appendix S2: Invasion condition in the diploid model with delayed inheritance

In the presence of delayed inheritance, a phenotype of an individual is determined by a maternal genotype. We therefore need to keep track the frequencies of 2×3 combination of phenotype $\times$ genotype to describe the genetic dynamics. Here we denote the two alleles as A (dominant allele) and a (recessive allele). An individual has either phenotype A or a (right-handed or left-handed, depending on which is dominant) that is determined by the genotype of its mother. We denote for example an individual with the genotype AA and the phenotype A by AA_A.

As we assume that A is a dominant allele and a is a recessive allele in the diploid model with delayed inheritance, the genotype-phenotype combination AA_a will never be produced (indeed, for an individual to have phenotype a, its mother should be homozygote of the recessive allele, aa). We denote the frequencies of AA_A, Aa_A, Aa_a, aa_A, and aa_a as x_A, y_A, y_a, z_A, and z_a. $x_a \equiv 0$ as noted above. The frequency of phenotype A is $x_A + y_A + z_A$ and that of phenotype a is $y_a + z_a$. Let p_i $(= x_i + y_i/2)$ be the frequency of allele A with phenotype i (= A or a), and q_i $(z_i + y_i/2)$ be the frequency of allele a with phenotype i (= A or a). The frequencies after mating are calculated from Table S1 as

$$
\begin{aligned}
T\tilde{x}_{\mathrm{A}} &= (p_{\mathrm{A}} + p_{\mathrm{a}})^2 - 2rp_{\mathrm{A}}p_{\mathrm{a}}, \\
T\tilde{y}_{\mathrm{A}} &= (p_{\mathrm{A}} + p_{\mathrm{a}})(q_{\mathrm{A}} + q_{\mathrm{a}}) + (p_{\mathrm{A}} + p_{\mathrm{a}})\frac{y_{\mathrm{A}} + y_{\mathrm{a}}}{2} - r(p_{\mathrm{A}}q_{\mathrm{a}} + p_{\mathrm{a}}q_{\mathrm{A}}) - \frac{r}{2}(p_{\mathrm{a}}y_{\mathrm{A}} + p_{\mathrm{A}}y_{\mathrm{a}}), \\
T\tilde{y}_{\mathrm{a}} &= (p_{\mathrm{A}} + p_{\mathrm{a}})(z_{\mathrm{A}} + z_{\mathrm{a}}) - r(p_{\mathrm{a}}z_{\mathrm{A}} + p_{\mathrm{A}}z_{\mathrm{a}}), \\
T\tilde{z}_{\mathrm{A}} &= (q_{\mathrm{A}} + q_{\mathrm{a}})\frac{y_{\mathrm{A}} + y_{\mathrm{a}}}{2} - \frac{r}{2}(q_{\mathrm{a}}y_{\mathrm{A}} + q_{\mathrm{A}}y_{\mathrm{a}}), \\
T\tilde{z}_{\mathrm{a}} &= (q_{\mathrm{A}} + q_{\mathrm{a}})(z_{\mathrm{A}} + z_{\mathrm{a}}) - r(q_{\mathrm{a}}z_{\mathrm{A}} + q_{\mathrm{A}}z_{\mathrm{a}}),
\end{aligned}
\tag{B1}
$$

where $T = 1 - 2r(x_{\mathrm{A}} + y_{\mathrm{A}} + z_{\mathrm{A}})(y_{\mathrm{a}} + z_{\mathrm{a}})$. When there is no reproductive isolation (r = 0) or viability selection (s = 0), the ratio of two phenotypes for the heterozygous genotype, $\mathrm{Aa_A}$: $\mathrm{Aa_a}$, is $(1 + p) : (1 - p)$ and that for the homozygous genotype, $\mathrm{aa_A}$: $\mathrm{aa_a}$, is $p : (1 - p)$ under delayed inheritance assuming the HW equilibrium.

(i) Invasibility of a dominant mutant

The frequencies in the next generation are then given by those after the viability selection favoring a dominant handedness mutant (A) with the selection coefficient s:

$$
x'_{\mathrm{A}} = \frac{(1+s)\tilde{x}_{\mathrm{A}}}{W},\ y'_{\mathrm{A}} = \frac{(1+s)\tilde{y}_{\mathrm{A}}}{W},\ y'_{\mathrm{a}} = \frac{\tilde{y}_{\mathrm{a}}}{W},\ z'_{\mathrm{A}} = \frac{(1+s)\tilde{z}_{\mathrm{A}}}{W},\ z'_{\mathrm{a}} = \frac{\tilde{z}_{\mathrm{a}}}{W}, \tag{B1}
$$

where $W = 1 + s(\tilde{x}_{\mathrm{A}} + \tilde{y}_{\mathrm{A}} + \tilde{z}_{\mathrm{A}})$ is the mean fitness of the population.

We now examine the invasibility of the dominant allele A in the resident population consisting only of the recessive allele a (i.e., $z_{\mathrm{a}} = 1$ and $x_{\mathrm{A}} = y_{\mathrm{A}} = y_{\mathrm{a}} = z_{\mathrm{A}} = 0$). The system **Error! Reference source not found.**-(B1) is linearized with respect to z_{A}, y_{A}, y_{a}, and x_{A} as

$$
\begin{pmatrix} z'_{\mathrm{A}} \\ y'_{\mathrm{a}} \\ y'_{\mathrm{A}} \\ x'_{\mathrm{A}} \end{pmatrix}
=
\begin{pmatrix}
0 & (1+s)/2 & (1-r)(1+s)/2 & 0 \\
0 & 1/2 & (1-r)/2 & 1-r \\
0 & (1+s)/2 & (1-r)(1+s)/2 & (1-r)(1+s) \\
0 & 0 & 0 & 0
\end{pmatrix}
\begin{pmatrix} z_{\mathrm{A}} \\ y_{\mathrm{a}} \\ y_{\mathrm{A}} \\ x_{\mathrm{A}} \end{pmatrix}, \tag{B2}
$$

where z_{a} is eliminated by using $z_{\mathrm{a}} = 1 - x_{\mathrm{A}} - y_{\mathrm{A}} - y_{\mathrm{a}} - z_{\mathrm{A}}$. The Jacobian matrix in the right hand side of (B2) has three zero eigenvalues and a non-trivial eigenvalue,

$$
\lambda = \frac{1}{2}(2 + s - r - rs). \tag{B3}
$$

The population allows the invasion of the dominant mutant if $\lambda > 1$, which gives exactly the same condition $(1-r)(1+s) > 1$ as that for the invasibility of dominant mutant if there was no delayed inheritance. Though the condition for the invasibility is the same, the value (B3)

itself is smaller than the dominant eigenvalue, $\lambda' = (1-r)(1+s)$, when there was no delayed inheritance, which corresponds to the fact that the delayed inheritance makes the invasion of a handedness mutant easier in a finite population.

(ii) Invasibility of a recessive mutant

Let us now consider the invasibility of a recessive handedness mutant that enjoys an ecological advantage in viability with the selection coefficient s. The frequencies after reproduction are given by **Error! Reference source not found.**, and the frequencies in the next generation are

$$x'_{\mathrm{A}} = \frac{\tilde{x}_{\mathrm{A}}}{W}, y'_{\mathrm{A}} = \frac{\tilde{y}_{\mathrm{A}}}{W}, y'_{\mathrm{a}} = \frac{(1+s)\tilde{y}_{\mathrm{a}}}{W}, z'_{\mathrm{A}} = \frac{\tilde{z}_{\mathrm{A}}}{W}, z'_{\mathrm{a}} = \frac{(1+s)\tilde{z}_{\mathrm{a}}}{W}, \tag{B4}$$

where $W = 1 + s(\tilde{y}_{\mathrm{a}} + \tilde{z}_{\mathrm{a}})$ is the mean fitness. As before $\tilde{x}_{\mathrm{a}} = 0$. The resident population consists only of dominant allele A (i.e., $x_{\mathrm{A}} = 1$ and $y_{\mathrm{A}} = y_{\mathrm{a}} = z_{\mathrm{A}} = z_{\mathrm{a}} = 0$). The system **Error! Reference source not found.**, (B4) is linearized with respect to z_{a}, z_{A}, y_{a}, and y_{A} as

$$\begin{aligned}
\begin{pmatrix} z'_{\mathrm{a}} \\ z'_{\mathrm{A}} \\ y'_{\mathrm{a}} \\ y'_{\mathrm{A}} \end{pmatrix} &= A \begin{pmatrix} z_{\mathrm{a}} \\ z_{\mathrm{A}} \\ y_{\mathrm{a}} \\ y_{\mathrm{A}} \end{pmatrix} + \begin{pmatrix} f_1(z_{\mathrm{a}}, z_{\mathrm{A}}, y_{\mathrm{a}}, y_{\mathrm{A}}) \\ f_2(z_{\mathrm{a}}, z_{\mathrm{A}}, y_{\mathrm{a}}, y_{\mathrm{A}}) \\ f_3(z_{\mathrm{a}}, z_{\mathrm{A}}, y_{\mathrm{a}}, y_{\mathrm{A}}) \\ f_4(z_{\mathrm{a}}, z_{\mathrm{A}}, y_{\mathrm{a}}, y_{\mathrm{A}}) \end{pmatrix} \\
&= \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ (1-r)(1+s) & 1+s & 0 & 0 \\ 1-r & 1 & 1-r & 1 \end{pmatrix} \begin{pmatrix} z_{\mathrm{a}} \\ z_{\mathrm{A}} \\ y_{\mathrm{a}} \\ y_{\mathrm{A}} \end{pmatrix} + \begin{pmatrix} f_1(z_{\mathrm{a}}, z_{\mathrm{A}}, y_{\mathrm{a}}, y_{\mathrm{A}}) \\ f_2(z_{\mathrm{a}}, z_{\mathrm{A}}, y_{\mathrm{a}}, y_{\mathrm{A}}) \\ f_3(z_{\mathrm{a}}, z_{\mathrm{A}}, y_{\mathrm{a}}, y_{\mathrm{A}}) \\ f_4(z_{\mathrm{a}}, z_{\mathrm{A}}, y_{\mathrm{a}}, y_{\mathrm{A}}) \end{pmatrix},
\end{aligned} \tag{B5}$$

where f_i's are quadratic or higher order terms of z_{a}, z_{A}, y_{a}, and y_{A}. The matrix A has eigenvalues $\lambda = 1$ and $\lambda = 0$ (with multiplicity 3). Because the dominant eigenvalue is 1, we need to construct a center manifold to examine the local stability of the equilibrium $(z_{\mathrm{a}}, z_{\mathrm{A}}, y_{\mathrm{a}}, y_{\mathrm{A}})^T = (0,0,0,0)^T$, where superscript T denotes the vector transform.

The eigenvector corresponding to the eigenvalue 1 is found, by solving $(A - 1I)\mathbf{b} = \mathbf{0}$, to be $\mathbf{b}_1 = (1,0,0,0)^T$, where I is a 4×4 identity matrix. There are two eigenvectors satisfying $(A - 0I)\mathbf{b} = A\mathbf{b} = \mathbf{0}$ corresponding to the eigenvalue 0:

$$\mathbf{b}_2 = \begin{pmatrix} 1 \\ -(1-r) \\ 0 \\ 0 \end{pmatrix}, \text{ and } \mathbf{b}_3 = \begin{pmatrix} 0 \\ 0 \\ 1 \\ -(1-r) \end{pmatrix}. \tag{B6}$$

We now find a nonzero vector $\mathbf{b}_4$ that, together with $\mathbf{b}_2$ and $\mathbf{b}_3$, spans the 3-dimensional generalized eigenspace corresponding to the eigenvalue 0. Such vector $\mathbf{b}_4$ must satisfy $(A-0I)^2\mathbf{b}_4 = A^2\mathbf{b}_4 = \mathbf{0}$ and be linearly independent of $\mathbf{b}_2$ or $\mathbf{b}_3$, which is obtained as

$$\mathbf{b}_4 = \begin{pmatrix} 1 \\ 0 \\ 0 \\ -(1-r)(2+s-r-rs) \end{pmatrix}. \tag{B7}$$

Now we define the transformation matrix P whose columns consist of $\mathbf{b}_1$, $\mathbf{b}_2$, $\mathbf{b}_3$, and $\mathbf{b}_4$:

$$P = \begin{pmatrix} 0 & 1 & 0 & 1 \\ 0 & -(1-r) & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 1 & 0 & -(1-r) & -(1-r)(2+s-r-rs) \end{pmatrix}. \tag{B8}$$

We then transform the variables as

$$\begin{pmatrix} z_{\mathrm{a}} \\ z_{\mathrm{A}} \\ y_{\mathrm{a}} \\ y_{\mathrm{A}} \end{pmatrix} = P \begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \end{pmatrix}. \tag{B9}$$

The dynamics for the transformed variables become

$$\begin{pmatrix} u_1' \\ u_2' \\ u_3' \\ u_4' \end{pmatrix} = P^{-1}AP\begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \end{pmatrix} + P^{-1}\begin{pmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \end{pmatrix}$$

$$= \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & (1-r)(1+s) \\ 0 & 0 & 0 & 0 \end{pmatrix}\begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \end{pmatrix} + \begin{pmatrix} F_1(u_1,u_2,u_3,u_4) \\ F_2(u_1,u_2,u_3,u_4) \\ F_3(u_1,u_2,u_3,u_4) \\ F_4(u_1,u_2,u_3,u_4) \end{pmatrix}. \tag{B10}$$

Here, $F_i(u_1,u_2,u_3,u_4)$ is the ith row of $P^{-1}\mathbf{f}(\mathbf{x}) = P^{-1}\mathbf{f}(P\mathbf{u})$ where $\mathbf{f} = (f_1, f_2, f_3, f_4)^T$, $\mathbf{x} = (z_a, z_A, y_a, y_A)^T$, and $\mathbf{u} = (u_1,u_2,u_3,u_4)^T$. We now define the center manifold

$$W^c = \{(u_1,u_2,u_3,u_4) \,|\, u_2 = f(u_1), u_3 = g(u_1), u_4 = h(u_1)\}, \tag{B11}$$

where f, g, and h are functions with the following properties: $f(0) = g(0) = h(0) = 0$ and $f'(0) = g'(0) = h'(0) = 0$. The simplest forms for such functions are $f(u) = au^2$, $g(u) = bu^2$, and $h(u) = cu^2$ where a, b, and c are constants. Substituting these into (B10), and requiring that the variables u_2', u_3', and u_4' in the next generation must lie on the center manifold ($u_2' = f(u_1')$, $u_3' = g(u_1')$, and $u_4' = h(u_1')$), we now have

$$\begin{aligned} u_1' &= u_1 + F_1(u_1, au_1^2, bu_1^2, cu_1^2), \\ a\left[u_1 + F_1(u_1, au_1^2, bu_1^2, cu_1^2)\right]^2 &= F_2(u_1, au_1^2, bu_1^2, cu_1^2), \\ b\left[u_1 + F_1(u_1, au_1^2, bu_1^2, cu_1^2)\right]^2 &= (1-r)(1+s)cu_1^2 + F_3(u_1, au_1^2, bu_1^2, cu_1^2), \\ c\left[u_1 + F_1(u_1, au_1^2, bu_1^2, cu_1^2)\right]^2 &= F_4(u_1, au_1^2, bu_1^2, cu_1^2). \end{aligned} \tag{B12}$$

The coefficients a, b, and c are determined from the leading order terms of the second to the forth equations of (B12) as

$$a = -\frac{1}{4(1-r)}, \quad b = \frac{1+s}{4}, \quad c = \frac{1}{4(1-r)}. \tag{B13}$$

Substituting this into the first equation of (B12), we have a slow dynamics on the center manifold:

$$u_1' = u_1 + \frac{1}{4}(s - r - rs)u_1^2 + O\left(u_1^3\right). \tag{B14}$$

Thus, u_1 converges to zero if and only if $s(1-r) - r < 0$ or $s < r/(1-r)$. Conversely, the recessive mutant can invade the population if $s > r/(1-r)$. This condition is the same as the condition $(2 + s - r - rs)/2 > 1$ or $(1-r)(1+s) > 1$ for the invasibility of the dominant mutant.

The center manifold $u_2 = -u_1^2/\left[4(1-r)\right]$, $u_3 = (1+s)u_1^2/4$, and $u_4 = u_1^2/\left[4(1-r)\right]$ in the original coordinate is defined in a parametric form with a parameter $\xi = u_1$ as

$$\begin{aligned} z_{\mathrm{a}} &= O\left(\xi^3\right), \\ z_{\mathrm{A}} &= \frac{1}{4}\xi^2 + O\left(\xi^3\right), \\ y_{\mathrm{a}} &= \frac{1+s}{4}\xi^2 + O\left(\xi^3\right), \\ y_{\mathrm{A}} &= \xi - \frac{3 + 2s - 2r - 2rs}{4}\xi^2 + O\left(\xi^3\right). \end{aligned} \tag{B15}$$

Appendix S3: Diffusion approximation analysis of the diploid model without delayed inheritance

We here derive the approximate one-dimensional diffusion process describing the allele frequency dynamics in a finite population of effective population size *N* without delayed inheritance. The discrete-generation genotype dynamics in infinite population are derived as (A1)-(A2) of Appendix S1. As is usual in diffusion approximation, we take the limit of weak fecundity and viability selections, $r \to 0$, $s \to 0$, and large population $N \to \infty$ with the products *Nr* and *Ns* being kept finite.

Assuming that both *s* and *r* are of the order of ε, a small positive constant, we expand the dynamics (A1)-(A2) in Taylor series with respect to ε. The leading order dynamics for the zygote frequencies *x*, *y*, and *z* of genotypes AA, Aa, and aa are then

$$\begin{aligned} x' &= p^2 + O(\varepsilon), \\ y' &= 2pq + O(\varepsilon), \\ z' &= q^2 + O(\varepsilon), \end{aligned} \tag{C1}$$

where $p = x + y/2$ and $q = z + y/2$ respectively is the frequency of allele A and a. Thus, in the leading order, genotype frequencies are in the Hardy-Weinberg equilibrium. From this it

also follows that the allele frequencies do not change with time, $p' = p$ and $q' = q$, up to the leading order.

Now we derive the slow allele frequency dynamics as the first order expansion of the equations (A1) and (A2). The change in the allele frequency p of the mutant allele A is then

$$\Delta p = p(1-p)\left\{r\left[p(2p^2-1)-h(6p^2-6p+1)\right]+s\left[p+h(1-2p)\right]\right\}+O(\varepsilon^2). \quad \text{(C2)}$$

Note that s in (C2) is the selection coefficient favoring the phenotype A. From (C2) we have the frequency dynamics:

$$\dot{p} = p(1-p)\left\{r\left[p(2p^2-1)-h(6p^2-6p+1)\right]+s\left[p+h(1-2p)\right]\right\}. \quad \text{(C3)}$$

The dynamics has two stable equilibria at p = 0 and p = 1, and an internal unstable equilibrium when $r > s$.

With random genetic drift, the diffusion process for the change in the allele frequency is characterized by infinitesimal mean and variance of the frequency change:

$$\begin{aligned} M(p) &= E\left[\Delta p | p\right] = p(1-p)\left\{r\left[p(2p^2-1)-h(6p^2-6p+1)\right]+s\left[p+h(1-2p)\right]\right\}, \\ V(p) &= E\left[(\Delta p)^2 | p\right] = \frac{p(1-p)}{2N}. \end{aligned} \quad \text{(C4)}$$

The fixation probability of the allele A with the initial frequency p then satisfies the backward equation (12) with the boundary condition $u(0)$ = 0 and $u(1)$ = 1. This yields equation (13). The fixation probability of a single mutant $\rho = u(1/2N)$ is then

$$\rho = \frac{1/(2N)}{\int_0^1 \exp\left\{4Nry(1-y)\left[\frac{y}{2}(1+y)-h(2y-1)\right]-4Nsy\left[\frac{y}{2}+h(1-y)\right]\right\}dy}, \quad \text{(C5)}$$

The relative fixation rate of a single mutant relative to that of a neutral mutant is given by $\phi = 2N\rho$:

$$\phi = \frac{1}{\int_0^1 \exp\left\{Ry(1-y)\left[\frac{y}{2}(1+y)-h(2y-1)\right]-Sy\left[\frac{y}{2}+h(1-y)\right]\right\}dy}, \quad \text{(C6)}$$

where $R = 4Nr$ and $S = 4Ns$. Here we consider three cases: (i) h = 0 (the recessive mutant), (ii) h = 1 (the dominant mutant), (iii) h = 0.5 (the partially dominant mutant).

(i) *h* = 0 (the recessive mutant)

After factorization, the deterministic dynamics is

$$\dot{p} = p^2(1-p)\left[r(2p^2-1)+s\right], \tag{C7}$$

when $h = 0$. This can be written as

$$\dot{p} = 2rp^2(1-p)\left(p-\sqrt{\frac{r-s}{2r}}\right)\left(p+\sqrt{\frac{r-s}{2r}}\right),$$

when $r > 0$ and $r > s$. Thus the dynamics has an internal unstable equilibrium at $p_c = \sqrt{(r-s)/2r}$ when $r > s$. When $s = 0$, therefore, the dynamics has two stable equilibria at $p = 0$ and $p = 1$, and an internal unstable equilibrium at $p_c = 1/\sqrt{2}$ (the dotted blue line in Fig. 3).

The relative fixation rate is

$$\phi_0 = \frac{1}{\int_0^1 \exp\left\{\frac{y^2}{2}\left[R(1-y^2)-S\right]\right\}dy}. \tag{C8}$$

When $s = 0$, for the relative fixation rate, $\phi_0 = 1/\int_0^1 \exp\left[\frac{Ry^2}{2}(1-y^2)\right]dy$, we can show the following properties. Firstly, at the limit of $R \to 0$ the fixation probability is equal to that of a neutral allele:

$$\phi_0\big|_{R=0} = 1. \tag{C9}$$

Secondly we see that $1/\phi_0$ is convex with respect to R because

$$\frac{\partial^2}{\partial R^2}\left(\frac{1}{\phi_0}\right) = \frac{1}{4}\int_0^1 \left(y^2-y^4\right)^2 \exp\left[\frac{R}{2}\left(y^2-y^4\right)\right]dy > 0. \tag{C10}$$

Thirdly we see that the sign of the initial slope of $1/\phi_0$ from

$$\frac{\partial}{\partial R}\left(\frac{1}{\phi_0}\right)\bigg|_{R=0} = \frac{1}{15}. \tag{C11}$$

Because the right-hand side of equation (C11) is positive, ϕ_0 is smaller than 1 for any $R > 0$. The fixation probability of a dominant mutant allele is always smaller than that, $1/(2N)$, of a neutral allele (i.e. the native recessive allele is the finite population size ESS, $\mathrm{ESS_N}$, in the sense of Nowak et al. (2004)). In addition, this value is smaller than the haploid model (1/12), implying that the reduction rate of fixation probability is more moderate in the diploid model.

(ii) *h* = 1 (the dominant mutant)

The frequency dynamics of dominant mutant is obtained from equation (C3):

$$\dot{p} = p(1-p)^2\left[-r\left(2p^2-4p+1\right)+s\right]. \tag{C12}$$

This can be written as

$$\dot{p} = 2rp(1-p)^2\left[p-\left(1-\sqrt{\frac{r+s}{2r}}\right)\right]\left[\left(1+\sqrt{\frac{r+s}{2r}}\right)-p\right].$$

If $r > s$, this has an internal unstable equilibrium at $p_c = 1-\sqrt{(r+s)/2r}$. When $s = 0$, the dynamics has an internal unstable equilibrium at $p_c = 1-1/\sqrt{2}$ (the dotted red line in Fig. 3).

Therefore the relative fixation rate of a recessive mutant to that of a neutral allele $\phi_1 = 2N\rho_1$ then satisfies

$$\phi_1 = \frac{1}{\int_0^1 \exp\left\{\frac{\gamma}{2}(2-y)\left[R(1-y)^2-S\right]\right\}dy}. \tag{C13}$$

If $s = 0$, we can show that the function $(1/\phi_1)$ is convex with respect to R, $\phi_1\big|_{R=0} = 1$, and $\left(\partial(1/\phi_1)/\partial R\right)\big|_{R=0} = 1/15$. Actually, ϕ_1 and ϕ_0 are equivalent ($\phi_0 = \phi_1$) when $s = 0$, though it is different when $s > 0$. This is obvious from equations (C8) and (C13); if we represent the frequency of the recessive allele as p and that of the dominant allele as q, then

$$\begin{aligned} p^2\left(1-p^2\right) &= (1-q)^2\left[1-(1-q)^2\right] \\ &= q(2-q)(1-q)^2. \end{aligned} \tag{C14}$$

(iii) *h* = 0.5 (the partially dominant mutant)

The frequency dynamics of mutant with partial dominance is obtained from equation (C3):

$$\dot{p} = \frac{1}{2}p(1-p)\left[r(2p-1)\left(2p^2-2p+1\right)+s\right]. \tag{C15}$$

This has an internal unstable equilibrium at

$$p_c = \frac{1}{2}+\frac{1}{2}\left(\sqrt{\frac{1}{27}+\left(\frac{s}{r}\right)^2}-\frac{s}{r}\right)^{\frac{1}{3}}-\frac{1}{6}\left(\sqrt{\frac{1}{27}+\left(\frac{s}{r}\right)^2}-\frac{s}{r}\right)^{-\frac{1}{3}},$$

when $r > s$. Equation (C15) has an internal unstable equilibrium at $p_c = 1/2$ when $s = 0$ (the dotted lime-green line in Fig. S1). The relative fixation rate is

$$\phi_2 = \frac{1}{\int_0^1 \exp\left\{\frac{y}{2}\left[R(1-2y+2y^2-y^3)-S\right]\right\}dy}. \tag{C16}$$

If $s = 0$, we can show that the function $(1/\phi_2)$ is convex with respect to R, $\phi_2\big|_{R=0} = 1$, and $\left(\partial(1/\phi_2)/\partial R\right)\big|_{R=0} = 1/15$.

These analytical expressions for the relative fixation rates ϕ_0, ϕ_1 and ϕ_2 obtained from one-dimensional diffusion approximation showed good agreements with the simulation results when N = 1,000 (Fig. 4H). When s = 0, we found that ϕ_0 and ϕ_1 are equivalent as shown in equation (C14) (Fig. 4H) and that ϕ_2 is higher than ϕ_0 and ϕ_1 when R is not small, implying that partial dominance can promote fixation of the mutant allele in the diploid model with three phenotypes (Figs. 4H, S2C).

Appendix S4: Diffusion approximation analysis of the diploid model with delayed inheritance

We here derive the approximate one-dimensional diffusion process describing the allele frequency dynamics of snail handedness alleles in a finite population of effective population size N with delayed inheritance. The discrete-generation genotype-phenotype dynamics in infinite population are derived as (B1) and (B2) or (B1) and (B5) of Appendix S2. As is usual in diffusion approximation, we take the limit of weak fecundity and viability selections, $r \to 0$, $s \to 0$, and large population $N \to \infty$ with the products Nr and Ns being kept finite.

Assuming that both s and r are of the order of ε, a small positive constant, we expand the dynamics (B1) and (B2)/(B5) in Taylor series with respect to ε. The leading order dynamics for the zygote frequencies $x = x_{\mathrm{A}} + x_{\mathrm{a}}$, $y = y_{\mathrm{A}} + y_{\mathrm{a}}$, $z = z_{\mathrm{A}} + z_{\mathrm{a}}$ of genotypes AA, Aa, and aa are then

$$\begin{aligned} x' &= p^2 + O(\varepsilon), \\ y' &= 2pq + O(\varepsilon), \\ z' &= q^2 + O(\varepsilon), \end{aligned} \tag{D1}$$

where $p = x + y/2$ and $q = z + y/2$ respectively is the frequency of allele A and a. Thus, in the leading order, genotype frequencies are in the Hardy-Weinberg equilibrium. From this it

also follows that the allele frequencies do not change with time, $p' = p$ and $q' = q$, up to the leading order. The frequencies of phenotype-genotype combinations are thus kept constant for a given allele frequency p (or q) up to the leading order:

$$\begin{aligned} x_{\mathrm{A}} &= p^2 + O(\varepsilon), \\ x_{\mathrm{a}} &= 0, \\ y_{\mathrm{A}} &= pq(1+p) + O(\varepsilon), \\ y_{\mathrm{a}} &= pq^2 + O(\varepsilon), \\ z_{\mathrm{A}} &= pq^2 + O(\varepsilon), \\ z_{\mathrm{a}} &= q^3 + O(\varepsilon). \end{aligned} \tag{D2}$$

Now we derive the slow allele frequency dynamics as the first order expansion of the equations (B1) and (B2)/(B5). The change in the allele frequency p of the dominant allele A is then

$$\Delta p = \frac{1}{2} p(1-p)^2 \left[-r(2p^2 - 4p + 1) - s \right] + O(\varepsilon^2). \tag{D3}$$

For the frequency q of the recessive allele, we have

$$\Delta q = \frac{1}{2} q^2 (1-q) \left[r(2q^2 - 1) + s \right] + O(\varepsilon^2). \tag{D4}$$

Note that s in (D3) and (D4) is the selection coefficient favoring phenotype a. If phenotype A is selected for, the sign must be changed before s in the right hand side of (D3) and (D4).

(i) The dominant mutant alleles

If the dominant mutant is selected for in the viability selection, we change the sign before s in the right hand side of (D3) to have the deterministic dynamics,

$$\dot{p} = \frac{1}{2} p(1-p)^2 \left[-r(2p^2 - 4p + 1) + s \right]. \tag{D5}$$

This rate of change in the allele frequency of dominant allele is exactly a half of that for the diploid model without delayed inheritance with $h = 1$ (eq. C12). In other words, the delayed inheritance does not change allele frequency dynamics at all except for its halved rate. Therefore, the position of internal unstable equilibrium, $p_c = 1 - 1/\sqrt{2}$, is the same as in the model without delayed inheritance (the solid red line in Fig. 3).

The relative fixation rate of a dominant mutant to that of a neutral allele $\phi_{\mathrm{A}} = 2N\rho_{\mathrm{A}}$ then satisfies

$$\phi_{\mathrm{A}} = \frac{1}{\int_0^1 \exp\left\{\frac{y}{4}(2-y)\left[R(1-y)^2 - S\right]\right\} dy}. \tag{D6}$$

(ii) The recessive mutant allele

If the recessive allele is selected for in the viability selection, we have from (D4) the deterministic dynamics,

$$\dot{q} = \frac{1}{2} q^2 (1-q)\left[r(2q^2-1)+s\right]. \tag{D7}$$

Again, the right hand side is exactly a half of that for the diploid model without delayed inheritance with $h = 0$ (eq. C7). Thus, two stable equilibria at $q = 0$ and $q = 1$, and an internal unstable equilibrium at $q_c = 1/\sqrt{2}$ are exactly the same as in the model without delayed inheritance (the solid blue line in Fig. 3). The relative fixation rate of a recessive mutant to that of a neutral allele $\phi_{\mathrm{a}} = 2N\rho_{\mathrm{a}}$ then satisfies

$$\phi_{\mathrm{a}} = \frac{1}{\int_0^1 \exp\left\{\frac{z^2}{4}\left[R(1-z^2)-S\right]\right\} dz}. \tag{D8}$$

Note that ϕ_{A} and ϕ_{a} are equivalent when $s = 0$, which can be shown by changing the variables in the integral in (D8) from z to $y = 1 - z$. When $s = 0$, the initial slope of $1/\phi_{\mathrm{A}}$ and $1/\phi_{\mathrm{a}}$ is $\left(\partial(1/\phi_{\mathrm{A}})/\partial R\right)\big|_{R=0} = 1/30$. This value is smaller than the haploid model (1/12) and the diploid model without delayed inheritance (1/15), implying that the reduction rate of fixation probability is more moderate in the diploid model with delayed inheritance.

The analytical formula for the relative fixation probabilities, (D6) and (D8), by one dimensional diffusion approximation showed good agreements with the Monte Carlo simulation results for the original 4 dimensional genotype-phenotype dynamics for sufficiently large N ($N = 1{,}000$, Fig. 4I).

Appendix S5: Exact fixation probabilities in the haploid model

We calculated exact fixation probabilities in the Markov process without any approximation by the first step analysis. Consider a finite population with N haploid individuals. Recursion equations of fixation probabilities can be written as

$$u(i) = \sum_{j=0}^{N} P_{i,j} u(j), \tag{E1}$$

where $u(i)$ is the probability that a mutant allele starting with i individuals in the initial population eventually goes to fixation, and $P_{i,j}$ is the transition probability that the number of mutant allele change from i to j in one generation ($0 \le i, j \le N$). Note that u here is a function of number of individuals, but u in Appendix S3 and S4 is a function of frequencies. With the boundary conditions $u(0) = 0$ and $u(N) = 1$, the fixation probability can be obtained by solving linear equations with $N - 1$ unknown variables. This can be written in a matrix form:

$$A\mathbf{u} = \mathbf{b}, \tag{E2}$$

where

$$A = \begin{pmatrix} P_{1,1} - 1 & P_{1,2} & \cdots & P_{1,(N-1)} \\ P_{2,1} & P_{2,2} - 1 & \cdots & P_{2,(N-1)} \\ \vdots & \vdots & \ddots & \vdots \\ P_{(N-1),1} & P_{(N-1),2} & \cdots & P_{(N-1),(N-1)} - 1 \end{pmatrix},$$

$$\mathbf{u} = \begin{pmatrix} u(1) \\ u(2) \\ \vdots \\ u(N-1) \end{pmatrix},$$

$$\mathbf{b} = \begin{pmatrix} -P_{1,N} \\ -P_{2,N} \\ \vdots \\ -P_{(N-1),N} \end{pmatrix}.$$

The solution can be obtained by multiplying the inverse of matrix A in the both sides of (E1): $\mathbf{u} = A^{-1}\mathbf{b}$. The transition probability $P_{i,j}$ is given by the binomial distribution when there is no selection ($r = s = 0$):

$$P_{i,j} = \binom{N}{j} p^j (1-p)^{N-j}, \tag{E3}$$

where $p = i/N$. When there is positive frequency-dependent selection due to reproductive isolation ($r > 0$ and $s = 0$), the expected frequency in the next generation in equation (E3), p, is replaced by equation (1):

$$P_{i,j} = \binom{N}{j} \left(\frac{p[1 - r(1-p)]}{1 - 2rp(1-p)} \right)^j \left(1 - \frac{p[1 - r(1-p)]}{1 - 2rp(1-p)} \right)^{N-j}. \tag{E4}$$

When there is viability selection for the mutant ($r > 0$ and $s > 0$), equation (E3) is replaced by

$$P_{i,j} = \binom{N}{j}\left(\frac{(1+s)\tilde{p}}{1+s\tilde{p}}\right)^{j}\left(1-\frac{(1+s)\tilde{p}}{1+s\tilde{p}}\right)^{N-j}, \qquad \text{(E5)}$$

where $\tilde{p}$ is from equation (1). The graphs of $u(1)$ are in good agreement with the simulation results when $N = 3$ (Fig. 4A).

One drawback of this method is that calculating the inverse matrix of the transition probability matrix, A, is time-consuming or almost impossible when N is large. In the diploid models, the dimension is two without delayed inheritance and four with delayed inheritance. Due to the 'curse of dimensionality,' therefore, calculation is especially difficult in the diploid models. For sufficiently small population size, however, this method is practical and gives accurate results for very small N when diffusion approximation fails.

Appendix S6: Exact fixation probabilities in the diploid model without delayed inheritance

Consider a finite population with diploid N individuals. The fixation probability can be calculated as

$$u(i,j) = \sum_{k=0}^{N}\sum_{l=0}^{N} P_{ij,kl}\, u(k,l), \qquad \text{(F1)}$$

where $u(i, j)$ is the fixation probability when there are i individuals of AA homozygote and j individuals of aa homozygote (we call this as state (i, j) hereafter) and $P_{ij,kl}$ is the transition probability from state (i, j) to state (k, l) in one generation ($0 \le i, j, k, l \le N$). Note that the number of heterozygous individuals Aa is $(N - i - j)$ or $(N - k - l)$. With the boundary conditions $u(0, N) = 0$ and $u(N, 0) = 1$ where the mutant allele is A and the wild-type allele is a, the fixation probability of a mutant allele, $u(0, N - 1)$, can be obtained by solving linear equations for $(N+1)(N+2)/2-2$ unknowns $u(i,j)$ for $i = 0,1,\cdots,N-1$, $j = 0,1,\cdots,N-1$, with $i + j \le N$. This can be rewritten in a matrix form $A\mathbf{u} = \mathbf{b}$:

$$\begin{pmatrix} P_{00,00}-1 & P_{00,01} & \cdots & P_{00,(N-1)1} \\ P_{01,00} & P_{01,01}-1 & \cdots & P_{01,(N-1)1} \\ \vdots & \vdots & \ddots & \vdots \\ P_{(N-1)1,00} & P_{(N-1)1,01} & \cdots & P_{(N-1)1,(N-1)1}-1 \end{pmatrix}\begin{pmatrix} u(0,0) \\ u(0,1) \\ \vdots \\ u(N-1,1) \end{pmatrix} = \begin{pmatrix} -P_{00,N0} \\ -P_{01,N0} \\ \vdots \\ -P_{(N-1)1,N0} \end{pmatrix}.$$

The solution is obtained by multiplying the inverse of matrix A in the both sides: $\mathbf{u} = A^{-1}\mathbf{b}$. The transition probability is given by the multinomial distribution,

$$P_{ij,kl} = \frac{N!}{k!(N-k-l)!l!}\left[\left(x+\frac{y}{2}\right)^2\right]^k\left[2\left(x+\frac{y}{2}\right)\left(\frac{y}{2}+z\right)\right]^{N-k-l}\left[\left(\frac{y}{2}+z\right)^2\right]^l, \quad \text{(F2)}$$

where $x = i/N$, $y = 1 - (i + j)/N$, and $z = j/N$. When there is positive frequency-dependent selection due to reproductive isolation or viability selection for the mutant in addition to reproductive isolation, the expected frequencies of genotypes in the next generation in equation (F2) is replaced by equation (A1) or (A2).

Appendix S7: Exact fixation probabilities in the diploid model with delayed inheritance

Consider a finite population with diploid N individuals. The fixation probability can be calculated as

$$u(a,b,c,d) = \sum_{i=0}^{N}\sum_{j=0}^{N}\sum_{k=0}^{N}\sum_{l=0}^{N} P_{abcd,ijkl}\, u(i,j,k,l), \quad \text{(G1)}$$

where $u(a, b, c, d)$ is the fixation probability when there are a individuals of AA_A, b individuals of Aa_A, c individuals of Aa_a, and d individuals of aa_A (we call this as state (a, b, c, d) hereafter) and $P_{abcd,ijkl}$ is the transition probability from state (a, b, c, d) to state (i, j, k, l) in one generation ($0 \le a, b, c, d, i, j, k, l \le N$). Note that the number of aa_a individuals is $(N - a - b - c - d)$ or $(N - i - j - k - l)$. The frequencies of AA_A, Aa_A, Aa_a, and aa_A are x_A (= a/N), y_A (= b/N), y_a (= c/N), z_A (= d/N). With the boundary conditions $u(0, 0, 0, 0) = u(0, 0, 0, 1) = \ldots = u(0, 0, 0, N) = 0$ and $u(N, 0, 0, 0) = 1$ where the dominant mutant allele is A and the recessive wild-type allele is a, the fixation probability of a mutant allele, $u(0, 0, 1, 0)$, can be obtained by solving linear equations for $u(i,j,k,l)$ with $i,j,k,l = 0,1,\cdots,N$ and $i+j+k+l \le N$. This can be rewritten in a matrix form $A\mathbf{u} = \mathbf{b}$:

$$\begin{pmatrix} P_{1000,1000}-1 & P_{1000,2000} & \cdots & P_{1000,00N0} \\ P_{2000,1000} & P_{2000,2000}-1 & \cdots & P_{2000,00N0} \\ \vdots & \vdots & \ddots & \vdots \\ P_{00N0,1000} & P_{00N0,2000} & \cdots & P_{00N0,00N0}-1 \end{pmatrix}\begin{pmatrix} u(1,0,0,0) \\ u(2,0,0,0) \\ \vdots \\ u(0,0,N,0) \end{pmatrix} = \begin{pmatrix} -P_{1000,N000} \\ -P_{2000,N000} \\ \vdots \\ -P_{00N0,N000} \end{pmatrix}.$$

The solution is obtained as: $\mathbf{u} = A^{-1}\mathbf{b}$. The transition probability is given by the multinomial distribution,

$$P_{abcd,ijkl} = \frac{N!}{i!j!k!l!(N-i-j-k-l)!}\bar{x}_A^i\bar{y}_A^j\bar{y}_a^k\bar{z}_A^l\left(1-\bar{x}_A-\bar{y}_A-\bar{y}_a-\bar{z}_A\right)^{N-i-j-k-l}, \text{(G2)}$$

where

$$\bar{x}_{\mathrm{A}} = \left(\frac{a}{N} + \frac{b+c}{2N}\right)^2,$$

$$\bar{y}_{\mathrm{A}} = \left(\frac{a}{N} + \frac{b+c}{2N}\right)\left(1 - \frac{a}{N}\right),$$

$$\bar{y}_{\mathrm{a}} = \left(\frac{a}{N} + \frac{b+c}{2N}\right)\frac{d+e}{N},$$

$$\bar{z}_{\mathrm{A}} = \frac{b+c}{2N}\left(\frac{b+c}{2N} + \frac{d+e}{N}\right).$$

The expected frequencies in the next generation in equation (G2) are replaced by equations (B1)-(B2) when there is positive frequency-dependent selection due to reproductive isolation and viability selection for the mutant.

When the recessive mutant allele is a and the wild-type allele is A, we solved the equation,

$$\begin{pmatrix} P_{1000,1000}-1 & P_{1000,2000} & \cdots & P_{1000,00N0} \\ P_{2000,1000} & P_{2000,2000}-1 & \cdots & P_{2000,00N0} \\ \vdots & \vdots & \ddots & \vdots \\ P_{00N0,1000} & P_{00N0,2000} & \cdots & P_{00N0,00N0}-1 \end{pmatrix} \begin{pmatrix} u(1,0,0,0) \\ u(2,0,0,0) \\ \vdots \\ u(0,0,N,0) \end{pmatrix} = \begin{pmatrix} -P_{1000,0000} \\ -P_{2000,0000} \\ \vdots \\ -P_{00N0,0000} \end{pmatrix},$$

to obtain the fixation probability of a single mutant, $u(N-1, 1, 0, 0)$, with the boundary conditions: $u(N, 0, 0, 0) = 0$ and $u(0, 0, 0, 0) = u(0, 0, 0, 1) = \ldots = u(0, 0, 0, N) = 1$. The expected frequencies in the next generation in equation (G2) are replaced by equations (B1) and (B5) when there is positive frequency-dependent selection due to reproductive isolation and viability selection for the mutant.

Appendix S8: The partial dominance model with two phenotypes

Thus far we considered the model in which h is a parameter that determines the intermediate phenotype of heterozygote (Appendix S1, S3). Here we consider the case where there are only two phenotypes (A and a) and the heterozygous phenotype is A with probability h and a with probability $1-h$. In this case, the mating probability between heterozygote (Aa × Aa) is

$$\left[h^2 + (1-h)^2 + 2h(1-h)(1-r)\right]y^2 = \left[1 - 2h(1-h)r\right]y^2. \qquad \text{(H1)}$$

Therefore the frequencies after mating are

$$T\dot{x} = x^2 + \left[1-(1-h)r\right]xy + \frac{1}{4}\left[1-2h(1-h)r\right]y^2,$$

$$T\dot{y} = \left[1-(1-h)r\right]xy + 2(1-r)xz + \frac{1}{2}\left[1-2h(1-h)r\right]y^2 + (1-hr)yz, \qquad \text{(H2)}$$

$$T\dot{z} = \frac{1}{4}\left[1-2h(1-h)r\right]y^2 + (1-hr)yz + z^2,$$

where $T = 1-2r(x+hy)\left[(1-h)y+z\right]$. This is the same as (A1) when h = 0 or 1. By linearizing the dynamics (H2) after viability selection (A2) for small x and y, we have the same result as equation (3) in Appendix S1. The largest eigenvalue of the linearized system is $(1 + hs)(1 - hr)$, and the mutant can invade if and only if $(1 + hs)(1 - hr) > 1$. This condition ($s > r/(1 - hr)$) is the same as the original diploid model (Appendix S1).

For diffusion approximation analysis, we take the limit of weak fecundity and viability selections, $r \to 0$, $s \to 0$, and large population $N \to \infty$ with the products Nr and Ns being kept finite (Appendix S3). Assuming that both s and r are the order of e, a small positive constant, the change in the allele frequency p of the mutant allele A is

$$\Delta p = p(1-p)\left[-p+h(2p-1)\right]\left\{r\left[1-2p^2-4hp(1-p)\right]-s\right\}+O(\varepsilon^2). \qquad \text{(H3)}$$

Note that s in (H3) is the selection coefficient favoring the phenotype A. From (H3) we have the frequency dynamics:

$$\dot{p} = p(1-p)\left[-p+h(2p-1)\right]\left\{r\left[1-2p^2-4hp(1-p)\right]-s\right\}. \qquad \text{(H4)}$$

When h = 1/2, this is a half of the haploid model (equation 8). The dynamics has two stable equilibria at p = 0 and p = 1, and an internal unstable equilibrium at $p_c = \frac{h}{2h-1} - \frac{\sqrt{(2h^2-2h+1)r+(2h-1)s}}{\sqrt{2r}(2h-1)}$ when $r > s$. The relative fixation rate of a single mutant relative to that of a neutral mutant is given by $\phi = 2N\rho$:

$$\phi = \frac{1}{\int_0^1 \exp\left\{\frac{y}{2}\left[y+2h(1-y)\right]\left[R(1-y)(1-2hy+y)-S\right]\right\}dy}. \qquad \text{(H5)}$$

where $R = 4Nr$ and $S = 4Ns$. As shown in Figure S3, the lowest fixation probability is obtained when h = 1/2. When h = 1/2, the fixation probability is exactly the same as the haploid model (Figs. 4G, 4H).

Exact fixation probabilities without approximation in small populations are also calculated as Appendix S6. Results are shown in Fig. 4B (the dotted dark-green line).

Literature Cited

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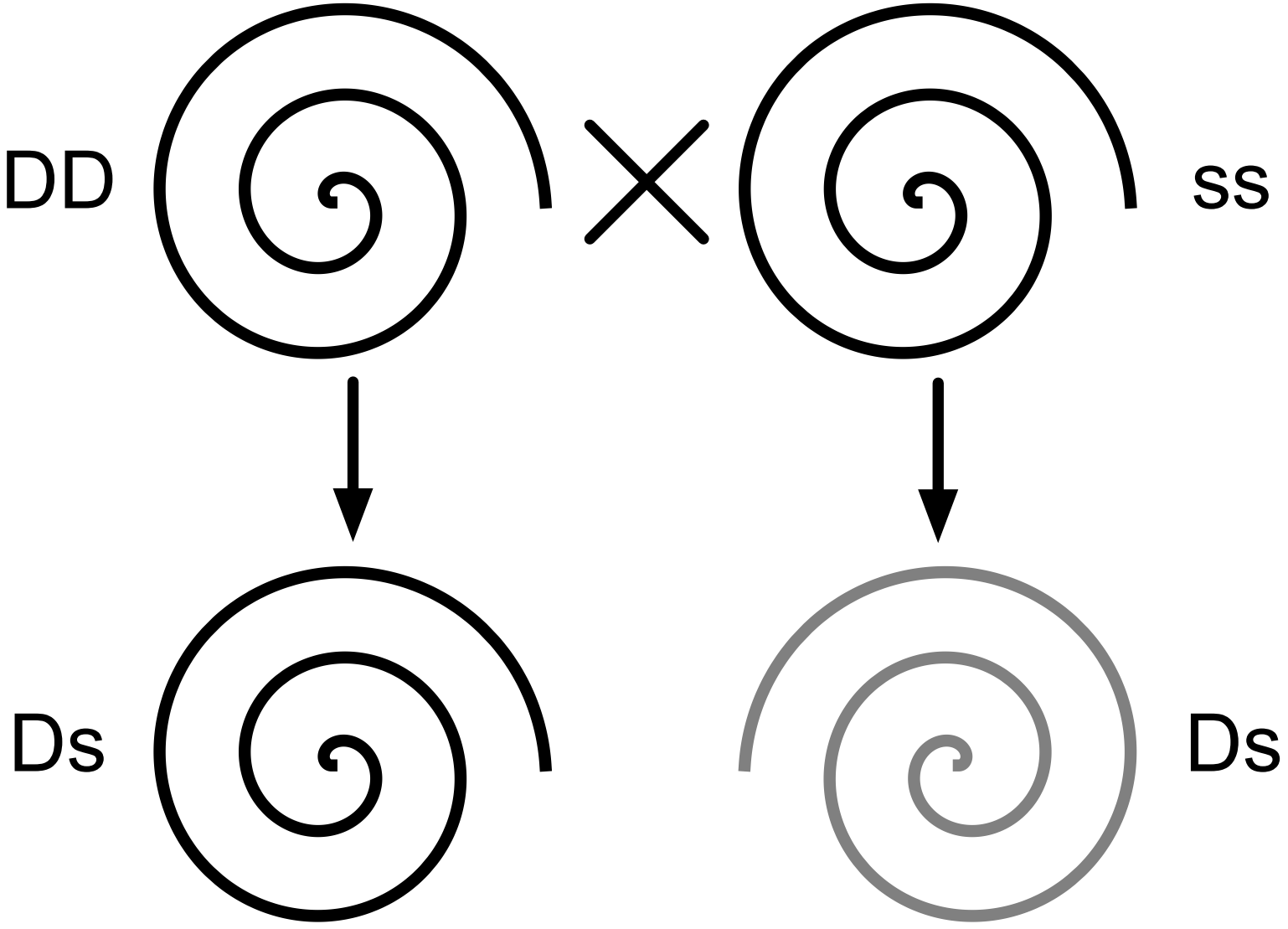
Nowak, M.A., Sasaki, A., Taylor, C., and Fudenberg, D. (2004) Emergence of cooperation and evolutionary stability in finite populations. Nature 428: 646-650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ss
Ds
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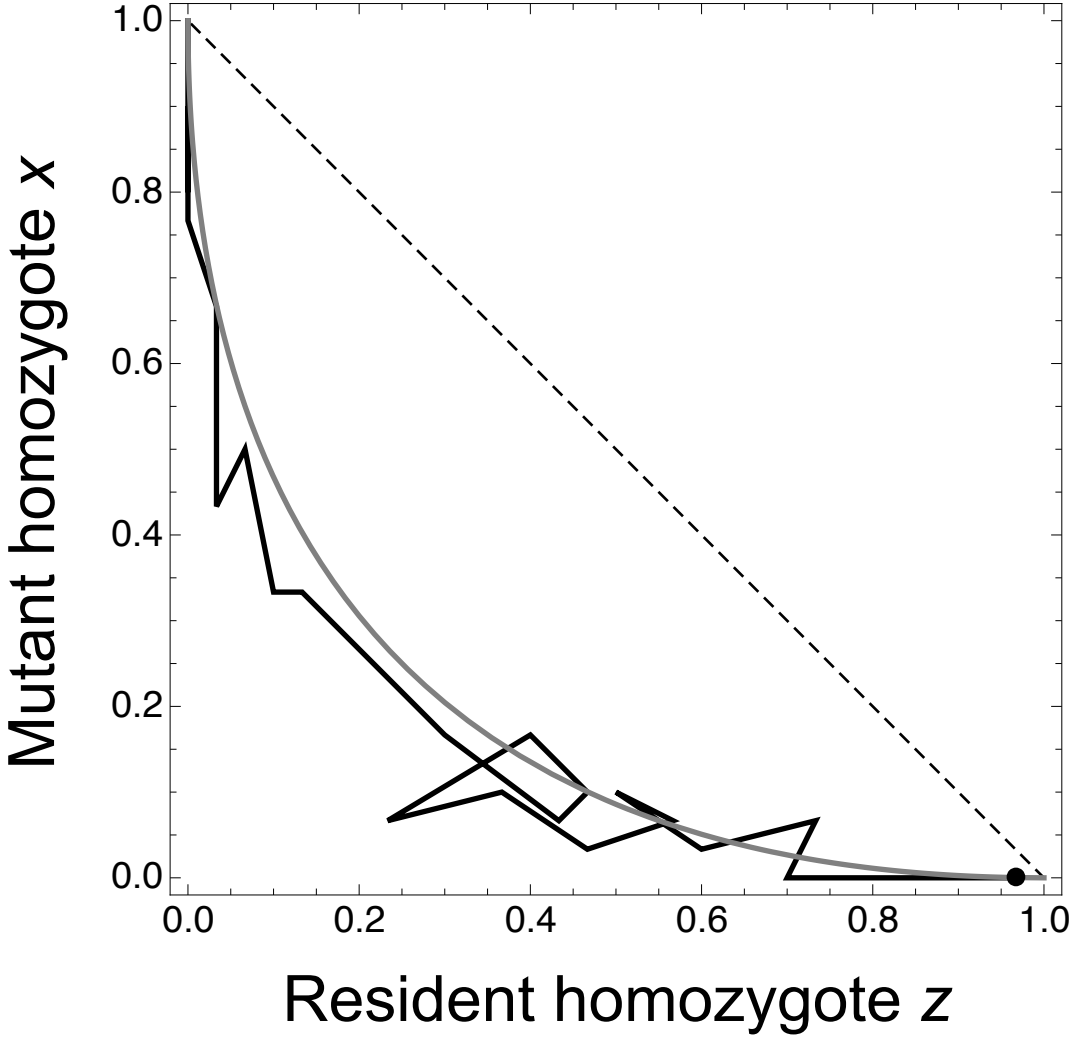
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Resident homozygote z
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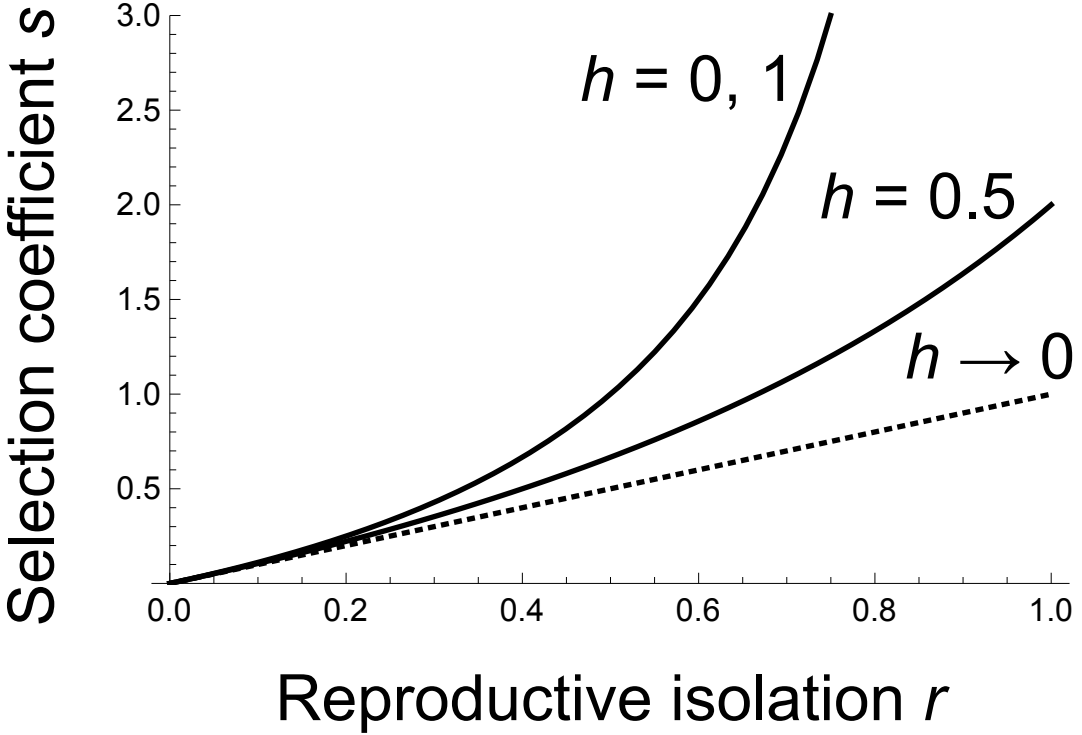
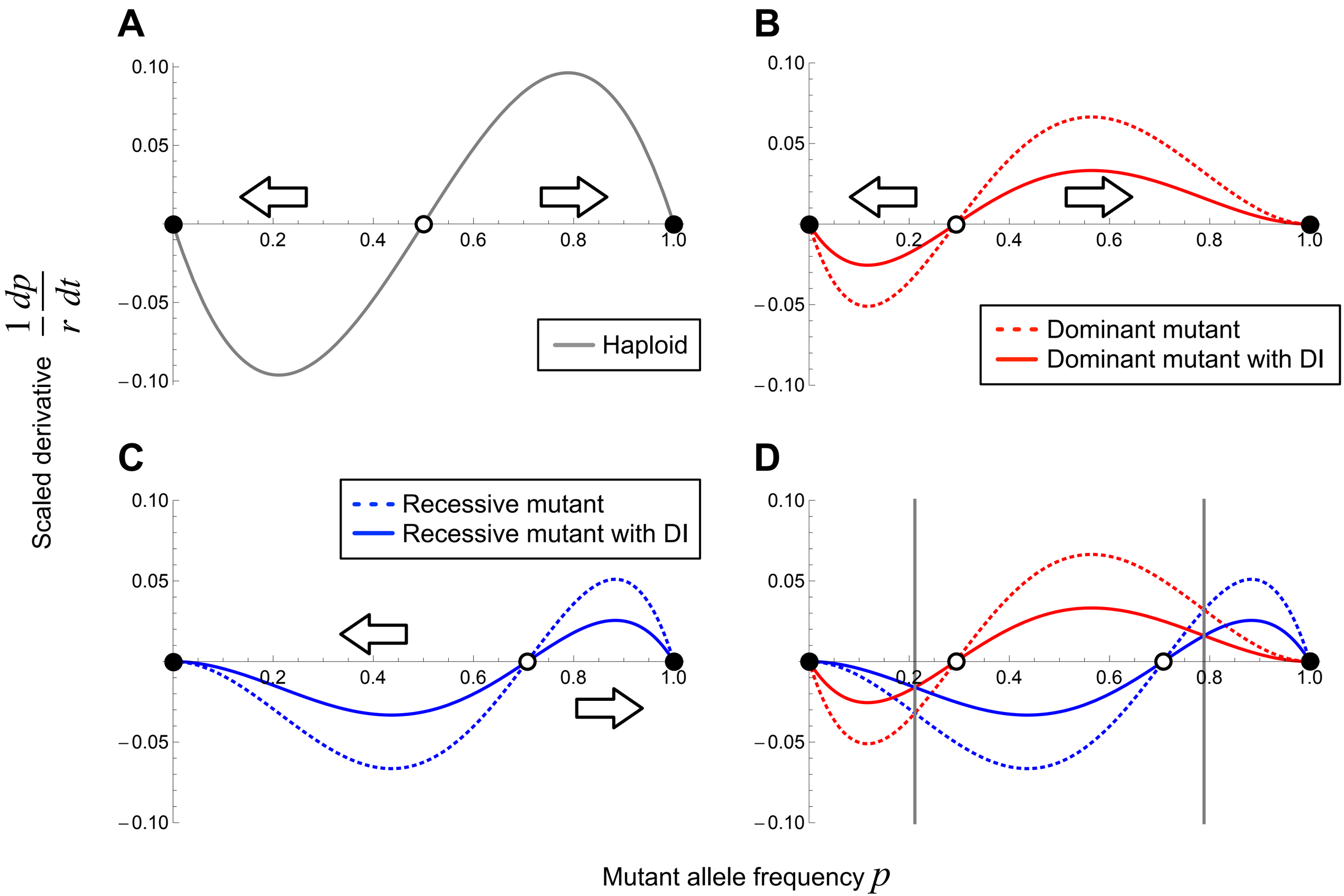
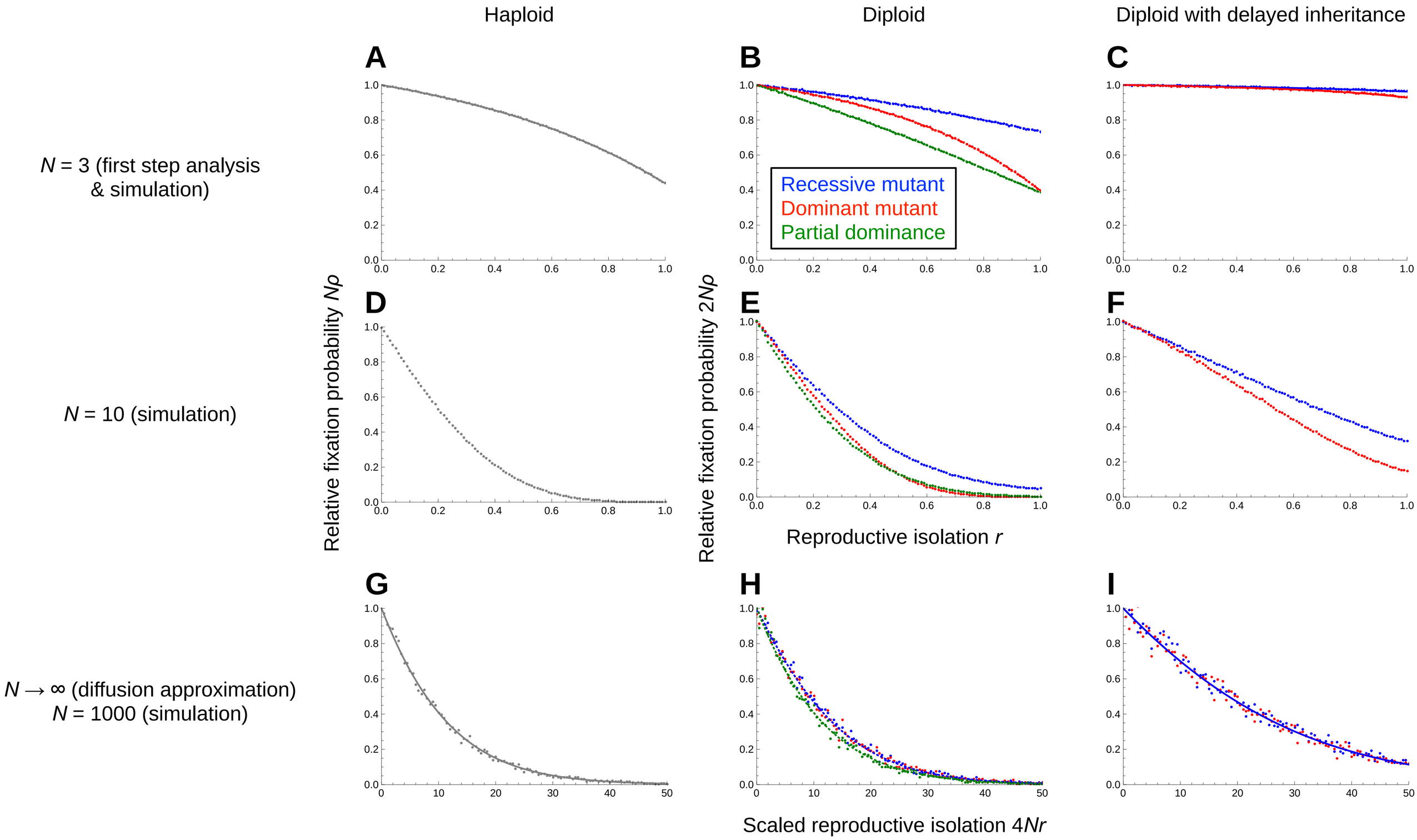
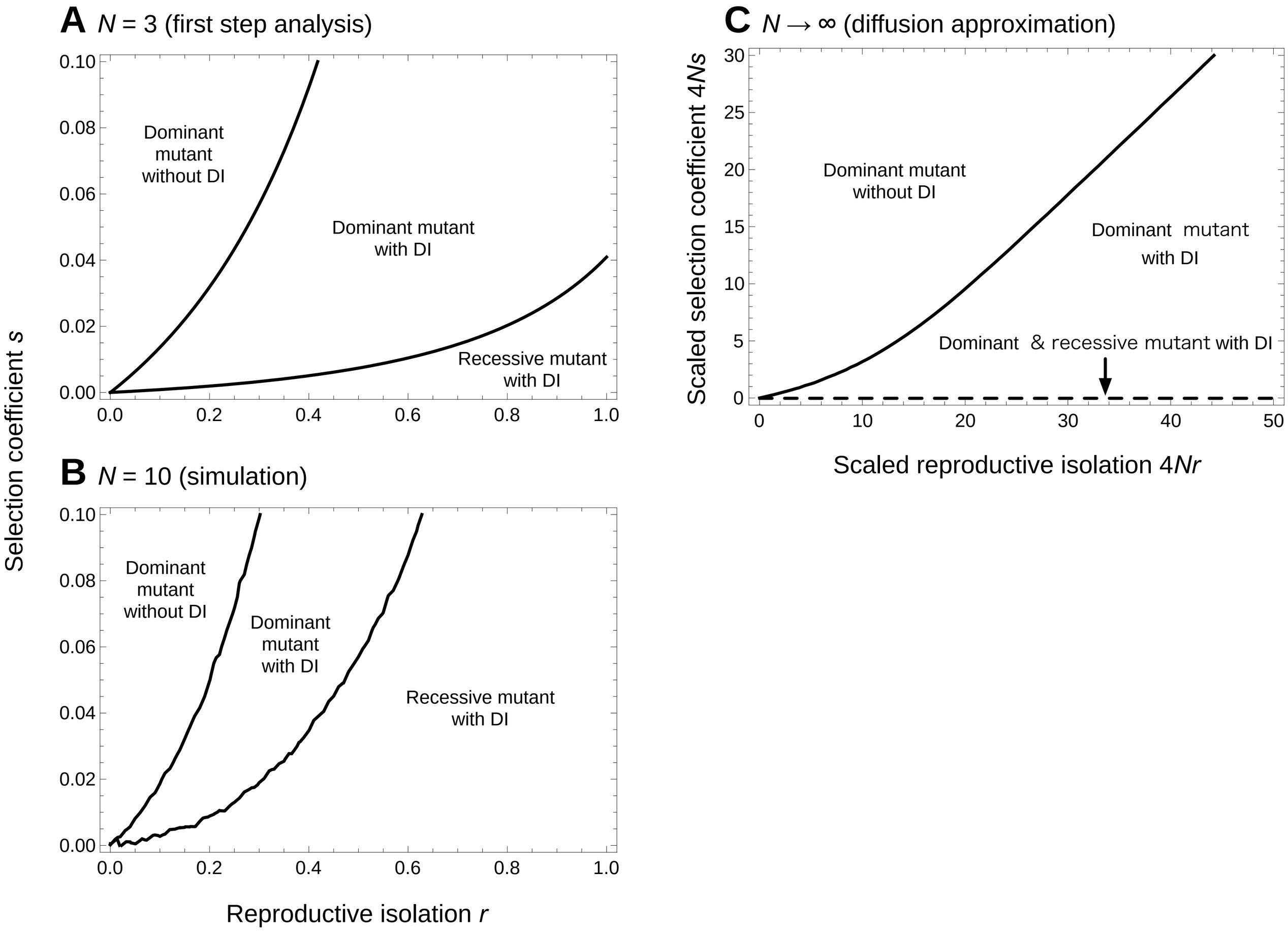
0.2
0.4
0.6
0.8
1.0


Selection coefficient s
3.0
2.5
2.0
1.5
1.0
0.5
h = 0, 1
h = 0.5
h → 0
0.0
0.2
0.4
0.6
0.8
1.0
Reproductive isolation r


A
B
C
D
Scaled derivative $\frac{1}{r}\frac{dp}{dt}$
Haploid
Dominant mutant
Dominant mutant with DI
Recessive mutant
Recessive mutant with DI
Mutant allele frequency p


Haploid
Diploid
Diploid with delayed inheritance
A
B
C
D
E
F
G
H
I
N = 3 (first step analysis & simulation)
N = 10 (simulation)
N → ∞ (diffusion approximation)
N = 1000 (simulation)
Relative fixation probability Np
Relative fixation probability 2Np
Recessive mutant
Dominant mutant
Partial dominance
Reproductive isolation r
Scaled reproductive isolation 4Nr


A N = 3 (first step analysis)
Dominant mutant without DI
Dominant mutant with DI
Recessive mutant with DI
B N = 10 (simulation)
Dominant mutant without DI
Dominant mutant with DI
Recessive mutant with DI
Selection coefficient s
Reproductive isolation r
C N → ∞ (diffusion approximation)
Dominant mutant without DI
Dominant mutant with DI
Dominant & recessive mutant with DI
Scaled selection coefficient 4Ns
Scaled reproductive isolation 4Nr

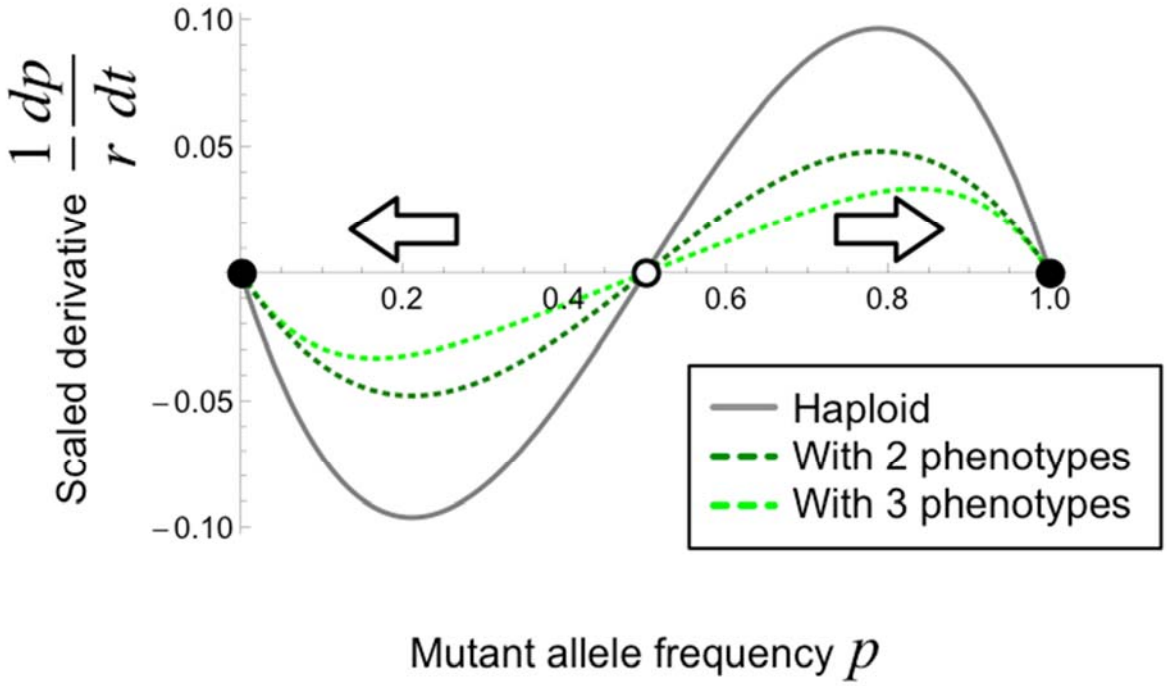


Figure S1: Allele frequency dynamics affected by positive frequency-dependent selection due to reproductive isolation (indicated by white arrows). *X*-axis: the mutant allele frequency (*p*). *Y*-axis: scaled derivatives of the mutant allele ($\dot{p}/r$). The haploid model (the solid gray line, eq. 8 when s = 0), the partial dominance model with two phenotypes (the dotted dark-green line, eq. H5 when s = 0 and h = 1/2), and the partial dominance model with three phenotypes (the dotted lime-green line, eq. 10 when s = 0 and h = 1/2). An unstable equilibrium at p = 1/2 (the white point) divides two basins of attraction. Stable equilibria are at p = 0 and 1 (the black points).

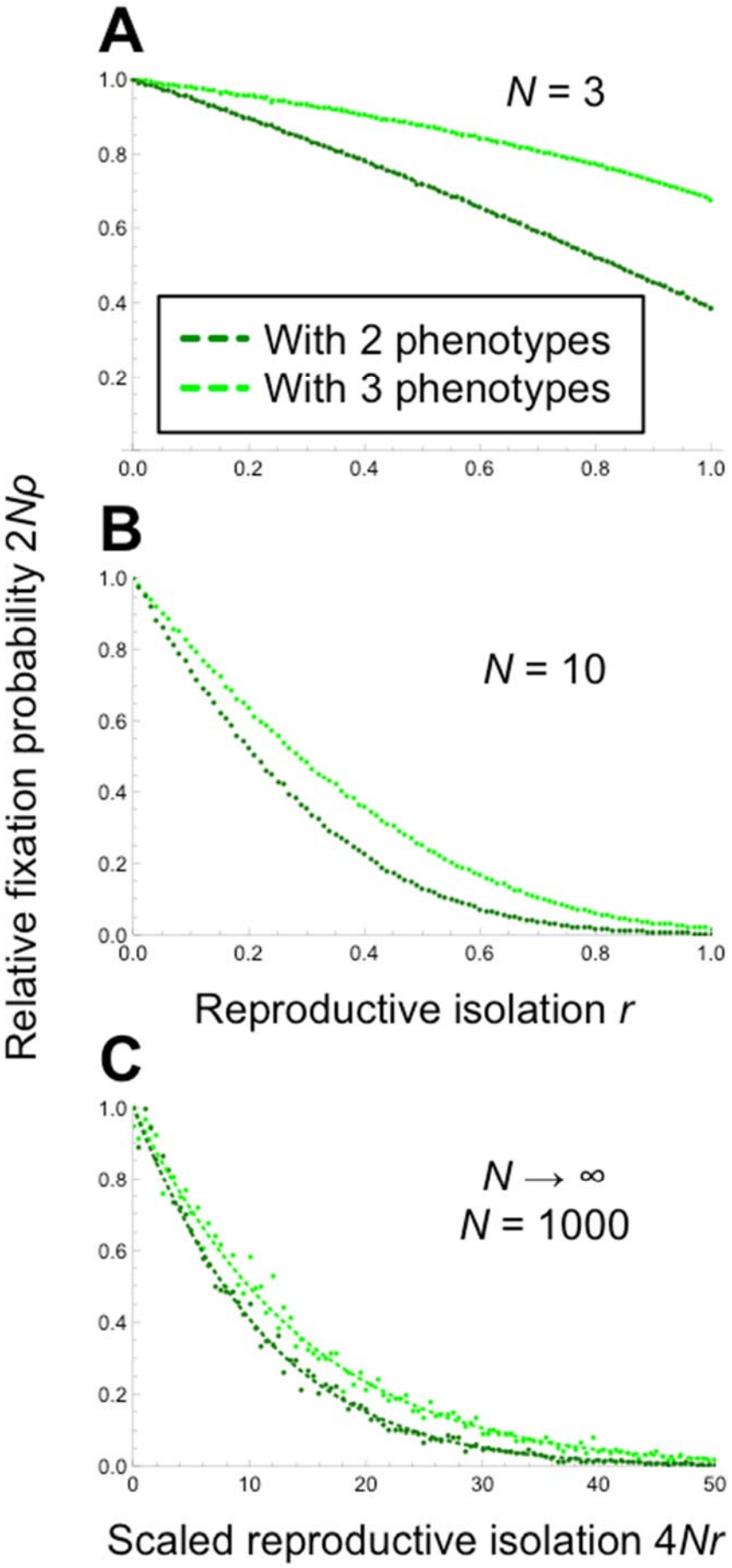

A
N = 3
With 2 phenotypes
With 3 phenotypes
B
N = 10
C
N → ∞
N = 1000
Relative fixation probability 2Np
Reproductive isolation r
Scaled reproductive isolation 4Nr

Figure S2: Relative fixation probabilities of a single mutant with reproductive isolation (and without viability selection: $s = 0$) to that of a neutral mutant. A, B: X-axis is the reproductive isolation parameter (r). C: X-axis is four times the product of the reproductive isolation parameter and the effective population size ($4Nr$). Y-axis is the product of fixation probability and effective population size ($2N\rho$). A: $N = 3$ (the first step analysis and Monte Carlo simulations), C: $N = 10$ (Monte Carlo simulations), C: $N \rightarrow \infty$ (diffusion approximation) and $N = 1000$ (Monte Carlo simulations). Dotted dark-green lines: the partial dominance model with two phenotypes. Dotted lime-green lines: the partial dominance model with three phenotypes.

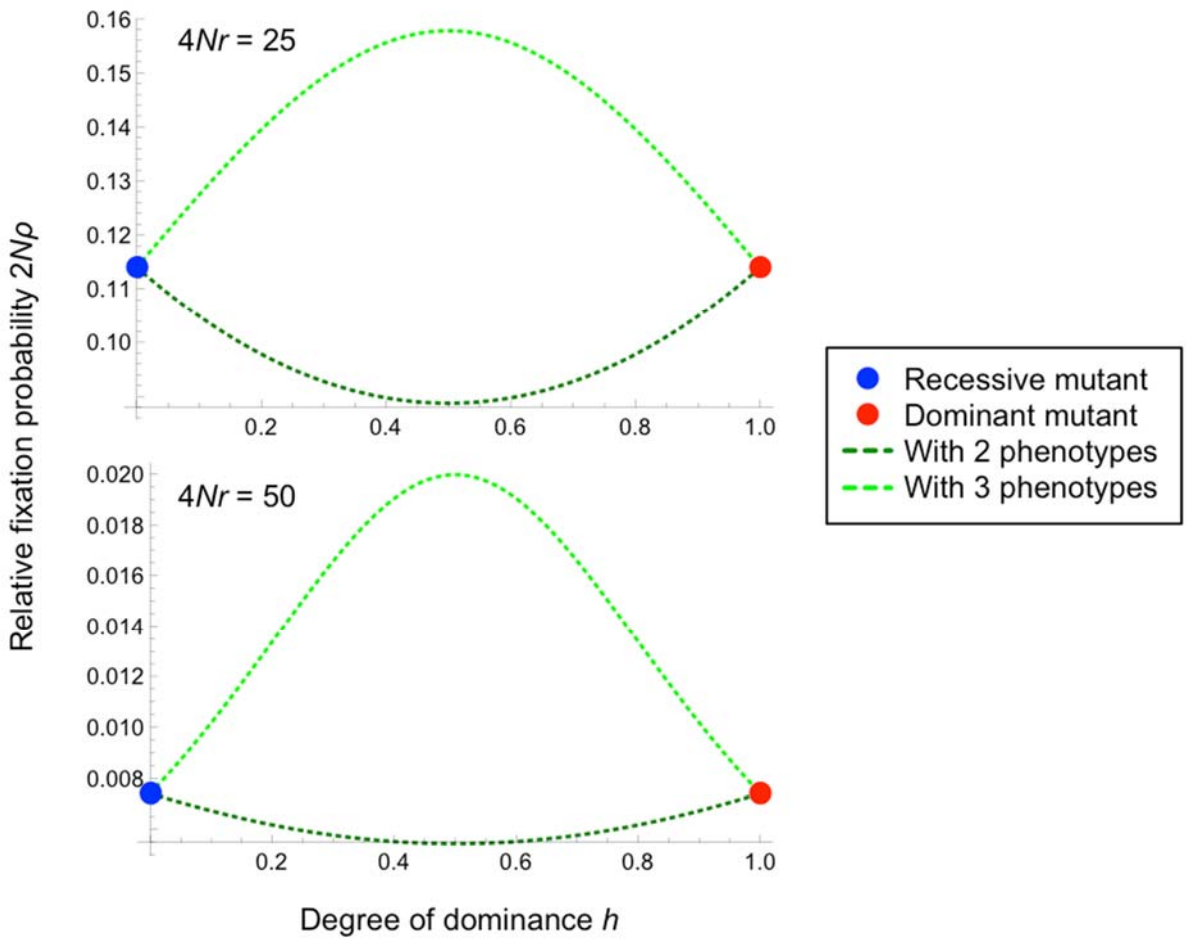


Figure S3: Effects of partial dominance in the diploid model without delayed inheritance in large populations. Blue points: the recessive mutant (h = 0). Red points: the dominant mutant (h = 1). Dotted dark-green lines: the partial dominance model with two phenotypes. Dotted lime-green lines: the partial dominance model with three phenotypes. When R (= $4Nr$) = 0, the fixation probability is 1 regardless of h values.

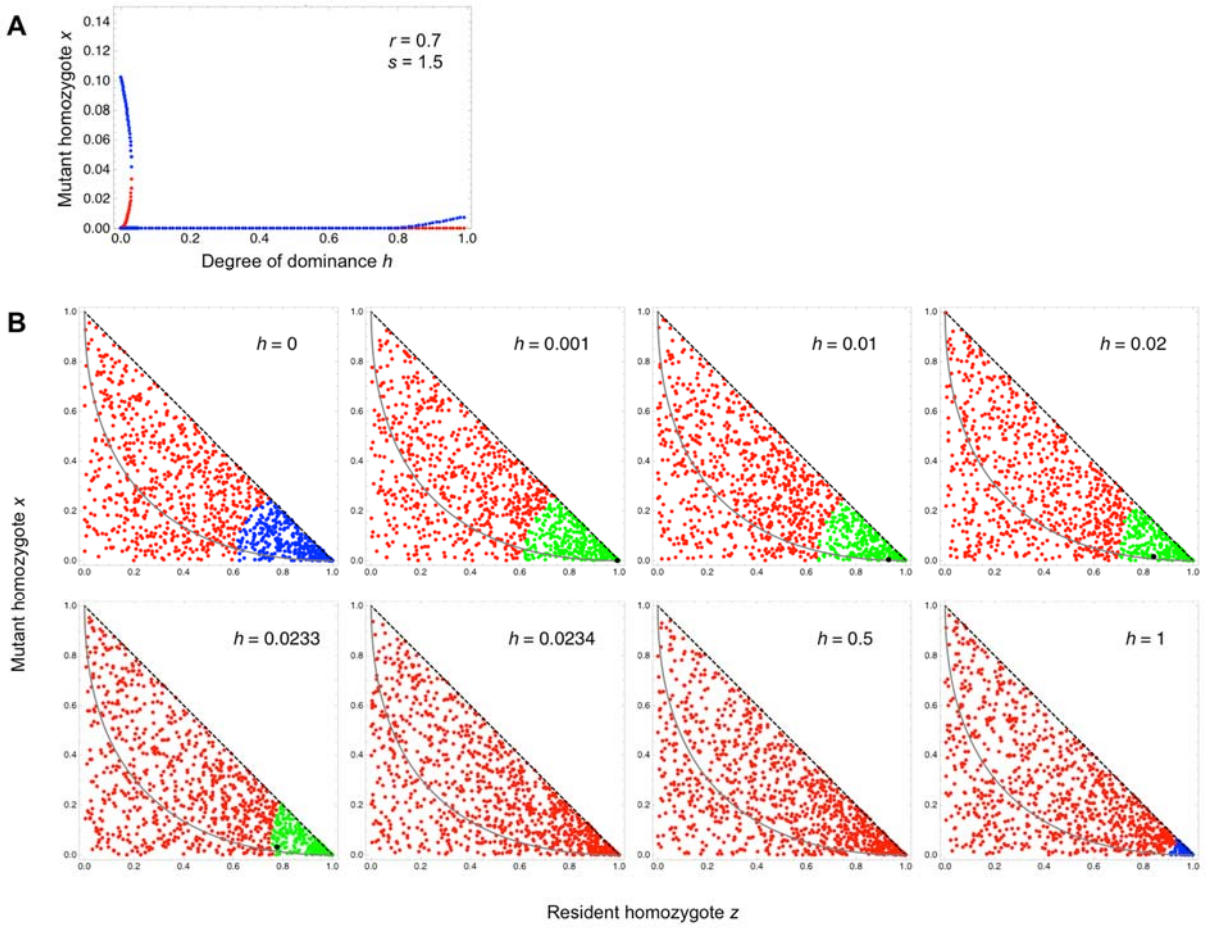


Figure S4: A: The bifurcation plot along the degree of dominance parameter (*h*). *Y*-axis is the frequency of the mutant homozygote (*x*). Red points: stable equilibria. Blue points: unstable equilibria. B: Simulation results of deterministic recursion equations (3)-(4). Red points: basin of attraction toward a stable equilibrium of the mutant allele. Blue points: basin of attraction toward a stable equilibrium of the resident allele. Green points: basin of attraction toward a stable equilibrium of both the mutant and resident alleles. The coexistence equilibria are shown as black points. The parameter condition is $r = 0.7$ and $s = 1.5$.

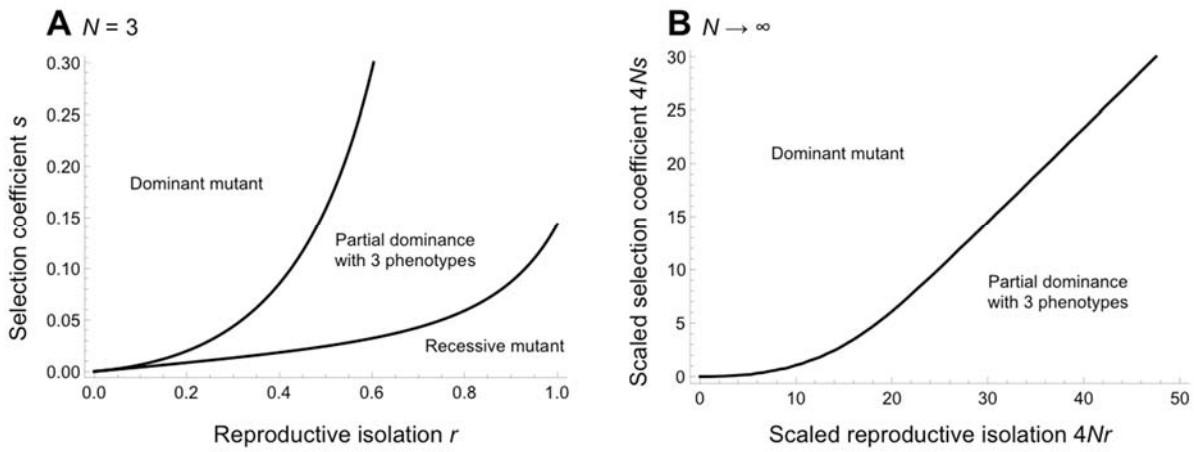


Figure S5: The alleles with the highest fixation probabilities in the diploid model without delayed inheritance given certain strength of reproductive isolation and viability selection. A: $N = 3$ (the first step analysis), B: $N \rightarrow \infty$ (diffusion approximation).

Table S1: The diploid model with delayed inheritance (when A is a dominant allele)

Mating comb.	Mating probability	AA_A	Aa_A	Aa_a	aa_A	aa_a
$AA_A \times AA_A$	x_A^2	1	0	0	0	0
$AA_A \times Aa_A$	$2x_A y_A$	1/2	1/2	0	0	0
$AA_A \times Aa_a$	$2(1-r)x_A y_a$	1/2	1/2	0	0	0
$AA_A \times aa_A$	$2x_A z_A$	0	1/2	1/2	0	0
$AA_A \times aa_a$	$2(1-r)x_A z_a$	0	1/2	1/2	0	0
$Aa_A \times Aa_A$	y_A^2	1/4	1/2	0	1/4	0
$Aa_A \times Aa_a$	$2(1-r)y_A y_a$	1/4	1/2	0	1/4	0
$Aa_A \times aa_A$	$2y_A z_A$	0	1/4	1/4	1/4	1/4
$Aa_A \times aa_a$	$2(1-r)y_A z_a$	0	1/4	1/4	1/4	1/4
$Aa_a \times Aa_a$	y_a^2	1/4	1/2	0	1/4	0
$Aa_a \times aa_A$	$2(1-r)y_a z_A$	0	1/4	1/4	1/4	1/4
$Aa_a \times aa_a$	$2y_a z_a$	0	1/4	1/4	1/4	1/4
$aa_A \times aa_A$	z_A^2	0	0	0	0	1
$aa_A \times aa_a$	$2(1-r)z_A z_a$	0	0	0	0	1
$aa_a \times aa_a$	z_a^2	0	0	0	0	1