

2 Taking only one and two-locus selection coefficients into account and assuming  
 3 no sex-of-origin effect of genes on fitness, equation 8 in the main text writes:

$$\begin{aligned}
 \frac{W}{\bar{W}} &= 1 + \sum_j a_j (\zeta_{j,\emptyset} + \zeta_{\emptyset,j}) + \sum_j a_{j,j} (\zeta_{j,j} - D_{j,j}) \\
 &+ \sum_{j<k} a_{jk} (\zeta_{jk,\emptyset} + \zeta_{\emptyset,jk} - 2\tilde{D}_{jk}) + \sum_{j<k} a_{j,k} (\zeta_{j,k} + \zeta_{k,j} - 2\tilde{D}_{j,k}) \\
 &+ \sum_{j<k} a_{j,k,j} (\zeta_{jk,j} + \zeta_{j,jk} - 2\tilde{D}_{jk,j}) + \sum_{j<k} a_{jk,k} (\zeta_{jk,k} + \zeta_{k,jk} - 2\tilde{D}_{jk,k}) \\
 &+ \sum_{j<k} a_{jk,jk} (\zeta_{jk,jk} - D_{jk,jk}).
 \end{aligned} \tag{A1}$$

4 We derive here expressions for these different  $a_{\mathbb{U},\mathbb{V}}$  coefficients under our three fitness  
 5 functions: uniformly deleterious alleles with fixed epistasis, Gaussian stabilizing selec-  
 6 tion acting on  $n$  quantitative traits, and stabilizing selection with non-Gaussian fitness  
 7 function (equations 9, 14 and 15 in the main text, respectively).

8  
 9 **Uniformly deleterious alleles.** Expressions for  $a_{\mathbb{U},\mathbb{V}}$  coefficients to the second order  
 10 in  $s$  and to the first order in epistatic coefficients ( $e_{\text{axa}}, e_{\text{axd}}, e_{\text{dxd}}$ ) are given in Appendix  
 11 A of Roze and Lenormand (2005), and can be obtained as follows. Assuming that  $s$  is  
 12 of order  $\epsilon$  (where  $\epsilon$  is a small term) and  $e_{\text{axa}}, e_{\text{axd}}, e_{\text{dxd}}$  are of order  $\epsilon^2$ , equation 9 may  
 13 be written as:

$$\begin{aligned}
 W &= 1 - \sum_j S_j + \sum_{j<k} \left[ S_j S_k + e_{\text{axa}} (X_j^{\text{M}} + X_j^{\text{P}}) (X_k^{\text{M}} + X_k^{\text{P}}) \right. \\
 &+ e_{\text{axd}} [(X_j^{\text{M}} + X_j^{\text{P}}) X_k^{\text{M}} X_k^{\text{P}} + (X_k^{\text{M}} + X_k^{\text{P}}) X_j^{\text{M}} X_j^{\text{P}}] \\
 &\left. + e_{\text{dxd}} X_j^{\text{M}} X_j^{\text{P}} X_k^{\text{M}} X_k^{\text{P}} \right] + o(\epsilon^2).
 \end{aligned} \tag{A2}$$

14 with

$$S_j = s [h (X_j^{\text{M}} + X_j^{\text{P}}) + (1 - 2h) X_j^{\text{M}} X_j^{\text{P}}] \tag{A3}$$

15 and where the last sum is over all pairs of loci  $j$  and  $k$  (counting each pair once). After  
 16 replacing  $X_j^M, X_j^P$  by  $\zeta_j^M + p_j, \zeta_j^P + p_j$  (and similarly for  $X_k^M, X_k^P$ ), expanding equation  
 17 A2 and using equation 5 in the main text, one obtains an expression for  $W$  in terms of  
 18  $\zeta_{\mathbb{U},\mathbb{V}}$  variables, where  $\mathbb{U}$  and  $\mathbb{V}$  take values in  $\{\emptyset, j, k, jk\}$ . Mean fitness  $\bar{W}$  is given by  
 19 the same expression, replacing  $\zeta_{\mathbb{U},\mathbb{V}}$  by  $D_{\mathbb{U},\mathbb{V}}$ . Expressing  $W/\bar{W}$  then yields equation 8  
 20 in the main text, where  $a_{\mathbb{U},\mathbb{V}}$  coefficients are given by (to the order  $\epsilon^2$ ):

$$a_{j,\emptyset} = -s [h + p_j (1 - 2h)] (1 + T_j) + \sum_k p_k [2e_{\text{axa}} + e_{\text{axd}} (2p_j + p_k) + e_{\text{dxd}} p_j p_k] \quad (\text{A4})$$

$$a_{j,j} = -s (1 - 2h) (1 + T_j) + \sum_k p_k (2e_{\text{axd}} + e_{\text{dxd}} p_k) \quad (\text{A5})$$

$$a_{jk,\emptyset} = a_{j,k} = e_{\text{axa}} + e_{\text{axd}} (p_j + p_k) + e_{\text{dxd}} p_j p_k \quad (\text{A6})$$

$$+ s^2 [h + p_j (1 - 2h)] [h + p_k (1 - 2h)]$$

$$a_{jk,j} = e_{\text{axd}} + e_{\text{dxd}} p_k + s^2 (1 - 2h) [h + p_k (1 - 2h)] \quad (\text{A7})$$

$$a_{jk,jk} = e_{\text{dxd}} + s^2 (1 - 2h)^2 \quad (\text{A8})$$

25 with:

$$T_j = s p_j [2h + p_j (1 - 2h)] + s (1 - 2h) \left( D_{j,j} + \sum_k D_{k,k} \right) \quad (\text{A9})$$

26 and where the sums are over all loci  $k$  different from  $j$ . Selection acting at a locus will  
 27 only have an effect when this locus is polymorphic, and  $a_{\mathbb{U},\mathbb{V}}$  coefficients with a ‘ $j$ ’ index  
 28 will thus be multiplied by  $p_j q_j$  in expressions describing changes in allele frequencies  
 29 and genetic associations due to selection. Assuming that deleterious alleles stay at low  
 30 frequency, we may neglect terms in  $p_j^2$ , and thus neglect the terms in  $p_j$  appearing  
 31 in expressions for  $a_{\mathbb{U},\mathbb{V}}$  coefficients with a ‘ $j$ ’ index. Furthermore, one can show that  
 32  $D_{j,j} = F p_j q_j$  to leading order (e.g., Roze, 2015), and equations A4 – A9 can thus be  
 33 simplified to:

$$a_{j,\emptyset} \approx -s h + [2e_{\text{axa}} - s^2 h (1 - 2h) F] \sum_k p_k \quad (\text{A10})$$

$$a_{j,j} \approx -s(1-2h) + [2e_{\text{axd}} - s^2(1-2h)^2 F] \sum_k p_k \quad (\text{A11})$$

34

$$a_{jk,\emptyset} = a_{j,k} \approx e_{\text{axa}} + s^2 h^2 \quad (\text{A12})$$

35

$$a_{jk,j} \approx e_{\text{axd}} + s^2 h(1-2h) \quad (\text{A13})$$

36

$$a_{jk,jk} \approx e_{\text{dxd}} + s^2(1-2h)^2. \quad (\text{A14})$$

37 These approximations also hold when  $s$ ,  $e_{\text{axa}}$ ,  $e_{\text{axd}}$  and  $e_{\text{dxd}}$  are all of order  $\epsilon$ , in which  
38 case the terms in  $s^2$  may be neglected in the expressions above.

39 Charlesworth et al. (1991) used the following fitness function to explore the ef-  
40 fects of synergistic epistasis on the mutation load and inbreeding depression in diploids:

$$W = e^{-\alpha n - \frac{\beta}{2} n^2} \quad (\text{A15})$$

41 where  $n = hn_{\text{he}} + n_{\text{ho}}$ ,  $n_{\text{he}}$  and  $n_{\text{ho}}$  being the number of heterozygous and homozygous  
42 mutations in the genome of the individual, respectively. Here we use a slightly modified  
43 version ensuring that the  $\beta$  term (representing epistasis) vanishes when only one locus  
44 carries a deleterious allele:

$$W = (1 - hs)^{n_{\text{he}}} (1 - s)^{n_{\text{ho}}} (1 - \beta h^2)^{\frac{1}{2}n_{\text{he}}(n_{\text{he}}-1)} (1 - \beta h)^{n_{\text{he}}n_{\text{ho}}} (1 - \beta)^{\frac{1}{2}n_{\text{ho}}(n_{\text{ho}}-1)}. \quad (\text{A16})$$

45 Equation A16 becomes equivalent to equation A15 (with  $\alpha = s$ ) when  $n_{\text{he}}$  and  $n_{\text{ho}}$  are  
46 large (so that  $n_{\text{he}} - 1 \approx n_{\text{he}}$  and  $n_{\text{ho}} - 1 \approx n_{\text{ho}}$ ), and when  $s$  and  $\beta$  are small. Assuming  
47 that  $s$  is of order  $\epsilon$  while  $\beta$  is of order  $\epsilon^2$ , equation A16 may be written as:

$$W = 1 - s \sum_j H_j + (s^2 - \beta) \sum_{j < k} H_j H_k + o(\epsilon^2) \quad (\text{A17})$$

48 with  $H_j = h(X_j^{\text{M}} + X_j^{\text{P}}) + (1 - 2h)X_j^{\text{M}}X_j^{\text{P}}$ . This yields the same expressions for  
49  $a_{\text{U,V}}$  coefficients as above, replacing  $e_{\text{axa}}$ ,  $e_{\text{axd}}$  and  $e_{\text{dxd}}$  by  $-\beta h^2$ ,  $-\beta h(1 - 2h)$  and

50  $-\beta(1-2h)^2$ , respectively. When using Charlesworth et al.'s (1991) fitness function  
 51 (equation A15), it can be shown that extra terms  $-\frac{\beta}{2}h^2$  and  $-(\frac{1}{2}-h^2)\beta$  appear in the  
 52 expressions of  $a_j$  and  $a_{j,j}$ , respectively. Figure 1D in the main text shows simulation  
 53 results obtained when fitness is given by equation A16, but simulations using equation  
 54 A15 gave very similar results (not shown).

55

56 **Gaussian stabilizing selection.** We now derive expression for  $a_{U,V}$  selection co-  
 57 efficients in the case of the multivariate, Gaussian fitness function given by equation  
 58 14 in the main text. In the following we assume weak selection, that is,  $g_\alpha^2/V_s$  is small,  
 59 of order  $\epsilon$ . A Taylor series of equation 14 to the second order in  $\epsilon$  yields:

$$W = 1 - \frac{\sum_\alpha g_\alpha^2}{2V_s} + \frac{1}{2} \left( \frac{\sum_\alpha g_\alpha^2}{2V_s} \right)^2 + o(\epsilon^2). \quad (\text{A18})$$

60 using equations 3 and 13 in the main text and assuming that mean trait values are  
 61 at the optimum ( $\bar{g}_\alpha = 2 \sum_j r_{\alpha j} p_j = 0$ ), we have  $g_\alpha = \sum_j r_{\alpha j} (\zeta_j^M + \zeta_j^P)$ , and equation  
 62 A18 can be written as:

$$\begin{aligned} W = & 1 + \sum_{j,k} b_{jk} (\zeta_{jk,\emptyset} + \zeta_{j,k} + \zeta_{k,j} + \zeta_{\emptyset,jk}) \\ & + \frac{1}{2} \sum_{j,k,l,m} b_{jk} b_{lm} (\zeta_{jklm,\emptyset} + \zeta_{jkl,m} + \zeta_{jkm,l} + \zeta_{jk,lm} \\ & + \zeta_{jlm,k} + \zeta_{jl,km} + \zeta_{jm,kl} + \zeta_{j,klm} \\ & + \zeta_{klm,j} + \zeta_{kl,jm} + \zeta_{km,jl} + \zeta_{k,jlm} \\ & + \zeta_{lm,jk} + \zeta_{l,jkm} + \zeta_{m,jkl} + \zeta_{\emptyset,jklm}) \Big] + o(\epsilon^2) \end{aligned} \quad (\text{A19})$$

63 where  $b_{jk} = -\sum_\alpha r_{\alpha j} r_{\alpha k} / (2V_s)$ , of order  $\epsilon$ . The first sum of equation A19 is over all  
 64 pairs of loci  $j$  and  $k$  (including  $j = k$ ), each pair with  $j \neq k$  being counted twice, while  
 65 the second sum is over all possible quadruplets of loci  $j, k, l, m$ . Mean fitness is given

66 by the same expression, replacing  $\zeta_{\mathbb{U},\mathbb{V}}$  by  $D_{\mathbb{U},\mathbb{V}}$ . To the second order in  $\epsilon$ , this yields:

$$\begin{aligned}
\frac{W}{\overline{W}} = & 1 + \sum_{j,k} b_{jk} \left[ \left( \zeta_{jk,\emptyset} + \zeta_{\emptyset,jk} - 2\tilde{D}_{jk} \right) + \left( \zeta_{j,k} + \zeta_{k,j} - 2\tilde{D}_{j,k} \right) \right] \\
& \times \left[ 1 - 2 \sum_{l,m} b_{lm} \left( \tilde{D}_{lm} + \tilde{D}_{l,m} \right) \right] \\
& + \frac{1}{2} \sum_{j,k,l,m} b_{jk} b_{lm} \left[ \left( \zeta_{jklm,\emptyset} + \zeta_{\emptyset,jklm} - 2\tilde{D}_{jklm} \right) + \left( \zeta_{jkl,m} + \zeta_{m,jkl} - 2\tilde{D}_{jkl,m} \right) \right. \\
& + \left( \zeta_{jkm,l} + \zeta_{l,jkm} - 2\tilde{D}_{jkm,l} \right) + \left( \zeta_{jlm,k} + \zeta_{k,jlm} - 2\tilde{D}_{jlm,k} \right) \\
& + \left( \zeta_{klm,j} + \zeta_{j,klm} - 2\tilde{D}_{klm,j} \right) + \left( \zeta_{jk,lm} + \zeta_{lm,jk} - 2\tilde{D}_{jk,lm} \right) \\
& \left. + \left( \zeta_{jl,km} + \zeta_{km,jl} - 2\tilde{D}_{jl,km} \right) + \left( \zeta_{jm,kl} + \zeta_{kl,jm} - 2\tilde{D}_{jm,kl} \right) \right] + o(\epsilon^2).
\end{aligned} \tag{A20}$$

67 Expressions for  $a_{\mathbb{U},\mathbb{V}}$  coefficients can be obtained by eliminating repeated indices in  
68  $\zeta_{\mathbb{U},\mathbb{V}}$  variables using the relation (e.g., eq. 5 in Kirkpatrick et al., 2002):

$$\zeta_{\mathbb{U}jj,\mathbb{V}} = p_j q_j \zeta_{\mathbb{U},\mathbb{V}} + (1 - 2p_j) \zeta_{\mathbb{U}j,\mathbb{V}} \tag{A21}$$

69 and finding the coefficient of  $\zeta_{\mathbb{U},\mathbb{V}}$  in equation A20 for each  $\mathbb{U}, \mathbb{V}$  (neglecting terms in-  
70 volving more than 2 loci). Using the fact that  $\tilde{D}_{jk}$  and  $\tilde{D}_{j,k}$  are of order  $\epsilon$  at equilibrium  
71 for  $j \neq k$ , one obtains:

$$a_{j,\emptyset} = \frac{a_{j,j}}{2} (1 - 2p_j) + o(\epsilon^2) \tag{A22}$$

$$a_{j,j} = 2b_{jj} \left[ 1 - 2 \sum_k b_{kk} (1 + F) p_k q_k \right] + \sum_k a_{jk,jk} p_k q_k + o(\epsilon^2) \tag{A23}$$

$$a_{jk,\emptyset} = a_{j,k} = 2b_{jk} + o(\epsilon) \tag{A24}$$

$$a_{jk,j} = \frac{a_{jk,jk}}{2} (1 - 2p_k) + o(\epsilon^2) \tag{A25}$$

$$a_{jk,jk} = 4 (b_{jj} b_{kk} + 2b_{jk}^2) + o(\epsilon^2). \tag{A26}$$

76 Note that the coefficient  $a_{jk,j}$  also includes a term  $12b_{jj}b_{jk} (1 - 2p_j)$ , but this term will  
77 vanish when summed over all  $j, k$  (and when computations are performed to the order

78  $\epsilon^2$ ), since the average of  $r_{\alpha k}$  over all loci is zero (no mutational bias).

79

80 **Non-Gaussian stabilizing selection.** We now derive two-locus  $a_{U,V}$  coefficients  
 81 in the more general case where fitness declines as  $d^Q$  with the distance  $d$  from the  
 82 phenotypic optimum (equation 15 in the main text). Weak selection implies that  
 83  $(g_\alpha^2/V_s)^{Q/2}$  is small, of order  $\epsilon$ . We will first derive expressions to the first order in  $\epsilon$ ,  
 84 and then to the second order. The derivations below assume that  $Q$  is an even integer;  
 85 however, simulations indicate that the approximations obtained may also hold when  
 86  $Q$  is odd (not shown). We have:

$$\begin{aligned} W &= 1 - \left( \frac{\sum_\alpha g_\alpha^2}{2V_s} \right)^{\frac{Q}{2}} + o(\epsilon) \\ &= 1 - \frac{1}{(2V_s)^{\frac{Q}{2}}} \sum_{\alpha, \beta, \gamma, \dots} \underbrace{g_\alpha^2 g_\beta^2 g_\gamma^2 \dots}_{\frac{Q}{2} \text{ elements}} + o(\epsilon). \end{aligned} \quad (\text{A27})$$

87 In the following we assume that average trait values are at the phenotypic optimum  
 88 ( $\bar{g}_\alpha = 0$ ), so that (from equation 13 in the main text)  $g_\alpha = \sum_i r_{\alpha i} (\zeta_j^M + \zeta_j^P)$ . We thus  
 89 have (to the first order in  $\epsilon$ ):

$$W = 1 - \frac{1}{(2V_s)^{\frac{Q}{2}}} \sum_{j, k, l, m, \dots} \left( \sum_{\alpha, \beta, \gamma, \dots} r_{\alpha j} r_{\alpha k} r_{\beta l} r_{\beta m} \dots \right) (\zeta_j^M + \zeta_j^P) (\zeta_k^M + \zeta_k^P) (\zeta_l^M + \zeta_l^P) \dots \quad (\text{A28})$$

90 where the first sum (over loci) comprises  $Q$  elements. From this, we obtain:

$$\frac{W}{\bar{W}} = 1 - \frac{1}{(2V_s)^{\frac{Q}{2}}} \sum_{j, k, l, m, \dots} \left( \sum_{\alpha, \beta, \gamma, \dots} r_{\alpha j} r_{\alpha k} r_{\beta l} r_{\beta m} \dots \right) \sum_{\mathbb{S} + \mathbb{T} = jklm \dots} (\zeta_{\mathbb{S}, \mathbb{T}} - D_{\mathbb{S}, \mathbb{T}}) + o(\epsilon) \quad (\text{A29})$$

91 where the last sum is over all possible partitions of the set of  $Q$  loci ( $jklm \dots$ ) into two  
 92 sets  $\mathbb{S}$  and  $\mathbb{T}$ . Using equation A21, one can see that the terms  $\zeta_{j, \emptyset}$ ,  $\zeta_{\emptyset, j}$  will necessarily  
 93 arise from terms in which all indices in  $\mathbb{S}$  and  $\mathbb{T}$  are repeated. For example for  $Q = 4$ ,

94 we have

$$\begin{aligned} \zeta_{jjkk,\emptyset} - D_{jjkk,\emptyset} &= (1 - 2p_j) p_k q_k \zeta_{j,\emptyset} + (1 - 2p_k) p_j q_j \zeta_{k,\emptyset} \\ &+ (1 - 2p_j) (1 - 2p_k) (\zeta_{jk,\emptyset} - D_{jk,\emptyset}), \end{aligned} \quad (\text{A30})$$

95

$$\begin{aligned} \zeta_{jj,kk} - D_{jj,kk} &= (1 - 2p_j) p_k q_k \zeta_{j,\emptyset} + (1 - 2p_k) p_j q_j \zeta_{\emptyset,k} \\ &+ (1 - 2p_j) (1 - 2p_k) (\zeta_{j,k} - D_{j,k}). \end{aligned} \quad (\text{A31})$$

96 Note that the terms  $\zeta_{jjjj,\emptyset} - D_{jjjj,\emptyset}$ ,  $\zeta_{jj,jj} - D_{jj,jj}$  will also generate terms in  $\zeta_{j,\emptyset}$ , but  
 97 we will neglect those based on the fact that they will be summed over a lower number  
 98 of loci (assuming that the number of loci is large). From this, the coefficient  $a_{j,\emptyset}$  is  
 99 given by (still for  $Q = 4$ ):

$$a_{j,\emptyset} = -\frac{2(1 - 2p_j)}{(2V_s)^2} \sum_k \sum_{\alpha,\beta} (r_{\alpha j}^2 r_{\beta k}^2 + 2r_{\alpha j} r_{\beta j} r_{\alpha k} r_{\beta k}) \times 2p_k q_k. \quad (\text{A32})$$

100 We can then note that  $2 \sum_k \sum_{\beta} r_{\beta k}^2 p_k q_k = n V_g^0$  (where  $V_g^0$  is the genic variance, the  
 101 same for all traits at equilibrium), while  $2 \sum_k r_{\alpha k} r_{\beta k} p_k q_k$  differs from zero only for  
 102  $\alpha = \beta$  (due to the fact that the average of  $r_{\alpha k}$  over all loci is zero) and equals  $V_g^0$  in  
 103 this case. Therefore,

$$a_{j,\emptyset} = -\frac{2(n + 2) V_g^0}{(2V_s)^2} \sum_{\alpha} r_{\alpha j}^2 (1 - 2p_j). \quad (\text{A33})$$

104 The same reasoning extends to other values of  $Q$  (as long as  $Q$  is even). In particular,  
 105 the factor 2 in equations A32 and A33 (that stemmed from the fact that both the terms  
 106  $\zeta_{j,\emptyset}$  and  $\zeta_{k,\emptyset}$  of equation A30 contribute to  $a_{j,\emptyset}$ ) becomes  $Q/2$ , while  $V_g^0$  in the same  
 107 equations becomes  $(V_g^0)^{\frac{Q}{2}-1}$ . The factor  $n + 2$  can be extended as follows. Consider  
 108 the term  $r_{\alpha j} r_{\alpha k} r_{\beta l} r_{\beta m} \dots$  in equation A29. Indices  $j, k, l \dots$  correspond to loci, that  
 109 have to be paired (in order to obtain repeated indices). A pair may occur “within the  
 110 same trait” (for example, the pair  $j = k$  is within the trait  $\alpha$ ) or “connect” two traits

111 (for example,  $j = l$  connects traits  $\alpha$  and  $\beta$ ), in which case these traits will have to  
 112 be the same when summing over loci (otherwise the sum equals zero). Two traits can  
 113 be connected, and disconnected from the other traits in two ways (for example,  $\alpha$  and  
 114  $\beta$  can be connected by  $j = l, k = m$  or by  $j = m, k = l$ ). Similarly, 3 traits can be  
 115 connected (and disconnected from the other traits) in 8 possible ways. For  $Q = 6$ ,  
 116  $(V_g^0)^2$  will thus be multiplied by a factor  $n^2 + 3 \times 2n + 8 = (n + 2)(n + 4)$  (the factor  
 117 3 stems from the fact that trait  $\alpha$  can be paired with  $\beta$ , or  $\alpha$  with  $\gamma$ , or  $\beta$  with  $\gamma$ . It  
 118 is possible to show by recursion that for higher values of  $Q$ , this factor becomes:

$$(n + 2)(n + 4) \dots (n + Q - 2) = \frac{2^{\frac{Q}{2}} \Gamma\left(\frac{Q+n}{2}\right)}{n \Gamma\left(\frac{n}{2}\right)}. \quad (\text{A34})$$

119 Therefore, we finally obtain:

$$a_j = -\frac{Q}{2nV_g^0} \left(\frac{V_g^0}{V_s}\right)^{\frac{Q}{2}} \frac{\Gamma\left(\frac{Q+n}{2}\right)}{\Gamma\left(\frac{n}{2}\right)} \sum_{\alpha} r_{\alpha j}^2 (1 - 2p_j). \quad (\text{A35})$$

120 Using a similar reasoning as above, one arrives at:

$$a_{j,j} = -\frac{Q}{nV_g^0} \left(\frac{V_g^0}{V_s}\right)^{\frac{Q}{2}} \frac{\Gamma\left(\frac{Q+n}{2}\right)}{\Gamma\left(\frac{n}{2}\right)} \sum_{\alpha} r_{\alpha j}^2. \quad (\text{A36})$$

121 Equations A35 can be used to compute the genic variance  $V_g^0$  at equilibrium under  
 122 random mating ( $\sigma = 0$ ), neglecting linkage disequilibria and other associations between  
 123 loci (see Supplementary File S2 for an expression when  $\sigma > 0$ ). Indeed, the change in  
 124  $p_j q_j = \tilde{D}_{jj}$  during selection (to the first order in  $\epsilon$ ) is given by:

$$\Delta_{\text{sel}} \tilde{D}_{jj} = a_j (1 - 2p_j) p_j q_j + o(\epsilon) \quad (\text{A37})$$

125 (see Supplementary File S2), while the change due to mutation is (to the first order  
 126 in  $u$ ):

$$\Delta_{\text{mut}} \tilde{D}_{jj} = u (1 - 2p_i)^2. \quad (\text{A38})$$



127 At mutation-selection balance, we thus have either  $p_j = 1/2$  (if selection is weak  
 128 relative to mutation), or

$$\frac{Q}{2nV_g^0} \left( \frac{V_g^0}{V_s} \right)^{\frac{Q}{2}} \frac{\Gamma(\frac{Q+n}{2})}{\Gamma(\frac{n}{2})} \sum_{\alpha} r_{\alpha j}^2 p_j q_j = u. \quad (\text{A39})$$

129 Summing the last expression over all loci yields:

$$\frac{Q}{2nV_g^0} \left( \frac{V_g^0}{V_s} \right)^{\frac{Q}{2}} \frac{\Gamma(\frac{Q+n}{2})}{\Gamma(\frac{n}{2})} \frac{nV_g^0}{2} = U \quad (\text{A40})$$

130 and thus:

$$\left( \frac{V_g^0}{V_s} \right)^{\frac{Q}{2}} \frac{\Gamma(\frac{Q+n}{2})}{\Gamma(\frac{n}{2})} = \frac{4U}{Q}. \quad (\text{A41})$$

131 From equations A35 – A36 and A41,  $a_j$  and  $a_{j,j}$  may be written as:

$$a_j = -\frac{2U}{nV_g^0} \sum_{\alpha} r_{\alpha j}^2 (1 - 2p_j) \quad (\text{A42})$$

132

$$a_{j,j} = -\frac{4U}{nV_g^0} \sum_{\alpha} r_{\alpha j}^2 \quad (\text{A43})$$

133 when mating is random. From equation 36 in the main text, and assuming that  
 134 most recombination rates between loci are sufficiently large relative to the strength  
 135 of selection  $a_j$ , the effect of purging on the spread of a selfing modifier (when  $\sigma = 0$ )  
 136 depends on the sum  $\sum_j a_j [a_j + a_{j,j} (1 - 2p_j)] p_j q_j$ . From equations A42 and A43, this  
 137 term equals  $6U^2 a^2 / V_g^0$ , where  $a^2$  is the variance of  $r_{\alpha j}$  across loci. Using the fact that  
 138 the average deleterious effect of a heterozygous mutation (in an optimal genotype) is  
 139 given by

$$\bar{s} = \left( \frac{a^2}{V_s} \right)^{\frac{Q}{2}} \frac{\Gamma(\frac{Q+n}{2})}{\Gamma(\frac{n}{2})} \quad (\text{A44})$$

140 (e.g., Gros et al., 2009) and using equation A41 yields equation 40 in the main text.

141 Coefficients  $a_{jk,\emptyset}$  and  $a_{j,k}$  are obtained as above. For  $Q = 4$ , terms in  $\zeta_{jk,\emptyset}$ ,  $\zeta_{j,k}$   
 142 arise in equations A30 – A31, but also from terms such as  $\zeta_{jkl,\emptyset} - D_{jkl,\emptyset}$ ,  $\zeta_{jk,ll} - D_{jk,ll}$ ,

143  $\zeta_{jll,k} - D_{jll,k}$ ,  $\zeta_{j,kll} - D_{j,kll}$  (with  $j \neq k \neq l$ ). Here again, we will neglect terms that are  
 144 summed over lower numbers of loci, and thus neglect the terms arising from equations  
 145 A30 – A31. Using the same reasoning as for  $a_j$ ,  $a_{j,j}$ , this yields:

$$a_{jk} = a_{j,k} = -\frac{Q}{nV_g^0} \left(\frac{V_g^0}{V_s}\right)^{\frac{Q}{2}} \frac{\Gamma\left(\frac{Q+n}{2}\right)}{\Gamma\left(\frac{n}{2}\right)} \sum_{\alpha} r_{\alpha j} r_{\alpha k} \quad (\text{A45})$$

146 and thus, using equation A41:

$$a_{jk} = a_{j,k} = -\frac{4U}{nV_g^0} \sum_{\alpha} r_{\alpha j} r_{\alpha k} \quad (\text{A46})$$

147 at mutation-selection balance when  $\sigma = 0$ , to leading order. Under random mating,  
 148 the linkage disequilibrium  $D_{jk}$  is given by:

$$D_{jk} \approx \frac{a_{jk}}{\rho_{jk}} p_j q_j p_k q_k \quad (\text{A47})$$

149 to leading order (see Supplementary File S2), and the effect of linkage disequilibria on  
 150 the genetic variance is thus:

$$2 \sum_{j \neq k} r_{\alpha j} r_{\alpha k} D_{jk} \approx -2U V_g^0 / (n \rho_H) \quad (\text{A48})$$

151 where  $\rho_H$  is the harmonic mean recombination rate between loci affecting the traits.  
 152 Furthermore, one obtains from equation A46

$$\sum_{j,k} a_{jk}^2 p_j q_j p_k q_k \approx \frac{4U^2}{n}, \quad (\text{A49})$$

153 independent of  $Q$ .

154 Coefficients  $a_{jk,j}$  and  $a_{j,k,jk}$  are also derived using the same method. For  $Q =$   
 155 4, the term  $\zeta_{jkk,j} - D_{jkk,j}$  appears twice in equation A29 and generate terms in  
 156  $(1 - 2p_k)(\zeta_{jk,j} - D_{jk,j})$ , while the term  $\zeta_{jk,jk} - D_{jk,jk}$  appears 4 times, yielding:

$$a_{jk,j} = -\frac{4}{(2V_s)^2} (1 - 2p_k) (S_{jj} S_{kk} + 2S_{jk}^2) \quad (\text{A50})$$

157

$$a_{jk,jk} = -\frac{8}{(2V_s)^2} (S_{jj}S_{kk} + 2S_{jk}^2) \quad (\text{A51})$$

158 with  $S_{jk} = \sum_{\alpha} r_{\alpha j} r_{\alpha k}$  (the extra factor 2 arises from the fact that each pair of loci  $j$ ,  
 159  $k$  is counted only once in equation A1, but twice in equation A29). Generalizing to  
 160 other (even) values of  $Q$ , one obtains:

$$a_{jk,j} = -\frac{Q(Q-2)}{2n(n+2)(V_g^0)^2} \left(\frac{V_g^0}{V_s}\right)^{\frac{Q}{2}} \frac{\Gamma\left(\frac{Q+n}{2}\right)}{\Gamma\left(\frac{n}{2}\right)} (1-2p_k) (S_{jj}S_{kk} + 2S_{jk}^2) \quad (\text{A52})$$

161

$$a_{jk,jk} = -\frac{Q(Q-2)}{n(n+2)(V_g^0)^2} \left(\frac{V_g^0}{V_s}\right)^{\frac{Q}{2}} \frac{\Gamma\left(\frac{Q+n}{2}\right)}{\Gamma\left(\frac{n}{2}\right)} (S_{jj}S_{kk} + 2S_{jk}^2). \quad (\text{A53})$$

162 Using equation A41, we thus have at mutation-selection balance and when  $\sigma = 0$ :

$$a_{jk,j} = -\frac{2U(Q-2)}{n(n+2)(V_g^0)^2} (1-2p_k) (S_{jj}S_{kk} + 2S_{jk}^2) \quad (\text{A54})$$

163

$$a_{jk,jk} = -\frac{4U(Q-2)}{n(n+2)(V_g^0)^2} (S_{jj}S_{kk} + 2S_{jk}^2). \quad (\text{A55})$$

164 In Supplementary File S2, we derive an expression for inbreeding depression in  
 165 a randomly mating population to the second order in  $U$ , under the fitness function  
 166 given by equation 15 in the main text. For this, the coefficients  $a_j$ ,  $a_{j,j}$  and  $a_{jk,jk}$  need  
 167 to be expressed to the second order in  $\epsilon$ . This can be achieved using the same method  
 168 as above, starting from:

$$W = 1 - \left(\frac{\sum_{\alpha} g_{\alpha}^2}{2V_s}\right)^{\frac{Q}{2}} + \frac{1}{2} \left(\frac{\sum_{\alpha} g_{\alpha}^2}{2V_s}\right)^Q + o(\epsilon^2). \quad (\text{A56})$$

169 Assuming random mating, this finally yields:

$$a_j = -\frac{Q}{2nV_g^0} [Z(Q, n) [1 + Z(Q, n)] - Z(2Q, n)] \sum_{\alpha} r_{\alpha j}^2 (1 - 2p_j) \quad (\text{A57})$$

170

$$a_{j,j} = -\frac{Q}{nV_g^0} [Z(Q, n) [1 + Z(Q, n)] - Z(2Q, n)] \sum_{\alpha} r_{\alpha j}^2 \quad (\text{A58})$$

171

$$\begin{aligned}
a_{jk,jk} = & - \frac{Q}{n(n+2)(V_g^0)^2} [(Q-2)Z(Q,n)[1+Z(Q,n)] - (2Q-2)Z(2Q,n)] \\
& \times (S_{jj}S_{kk} + 2S_{jk}^2)
\end{aligned}
\tag{A59}$$

172 with:

$$Z(Q,n) = \left(\frac{V_g^0}{V_s}\right)^{\frac{Q}{2}} \frac{\Gamma\left(\frac{Q+n}{2}\right)}{\Gamma\left(\frac{n}{2}\right)}.
\tag{A60}$$

173 It can be verified that equations A57 – A59 are equivalent to equations A22, A23 and  
174 A26 in the case of a Gaussian fitness function ( $Q = 2$ ) and under random mating  
175 ( $\sigma = 0$ ).

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