

1

2

3 **Supplementary Figure 1. The process of amplifying and generating focal hemiclones**

4 **used in male and female fitness measurements.** By sampling random wild-type males from

5 LH_M to initiate the first wild-type (wt) x clone-generator (cg) cross, multiple hemiclone

6 lines—each carrying a random and unique X-2-3 chromosomal complement, or “target

7 genomes” (tg)—from LH_M are thus generated. A further cross of these hemiclone tg males to

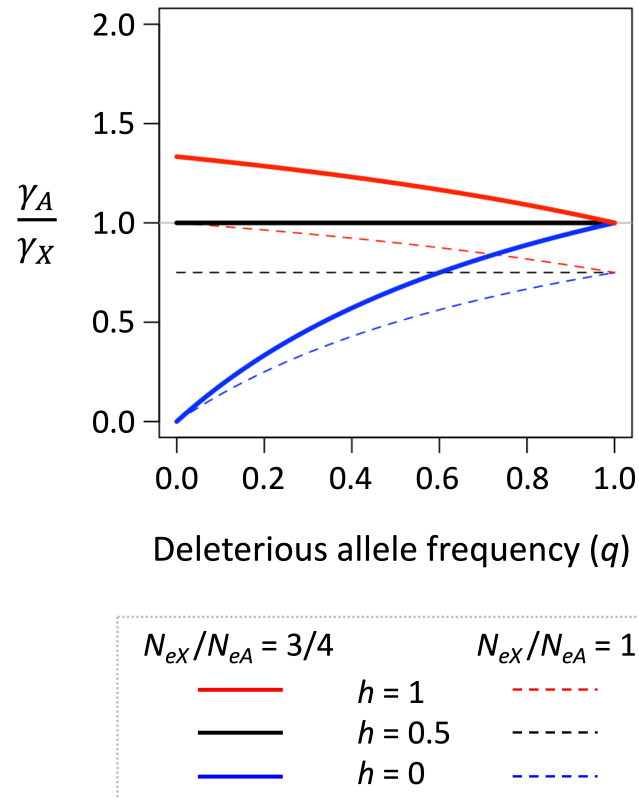
8 either wild-type females or fused-X females produces “focal” hemiclone females and males,

9 respectively. Measurements of fitness were performed on these individuals (as described in

10 Ruzicka *et al.* 2019). See Abbott and Morrow (2011) for further details on the hemiclone

11 amplification process.

12



13

14 **Supplementary Figure 2. Effects of dominance and effective population size on the**

15 **efficacy of purifying selection at autosomal versus X-linked loci.** The relative efficacy of

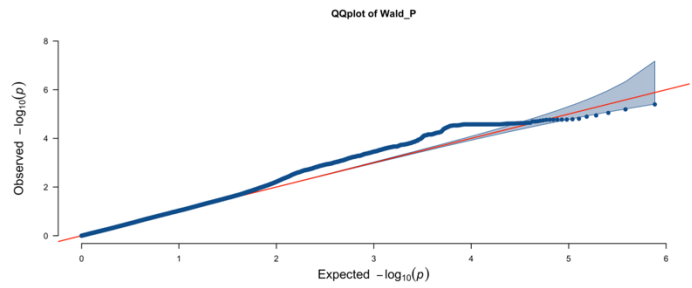
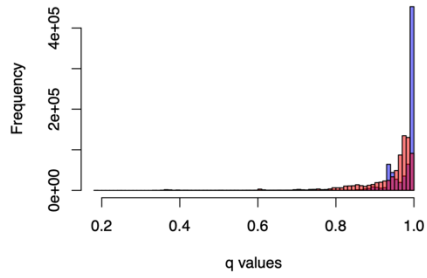
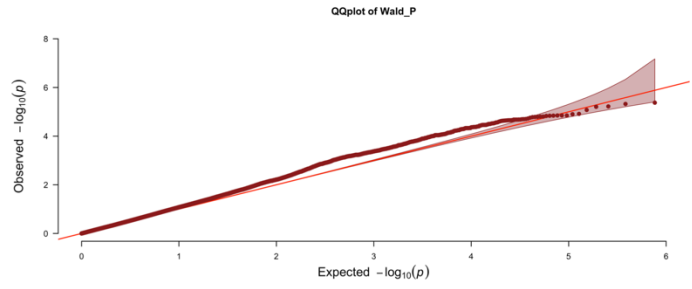
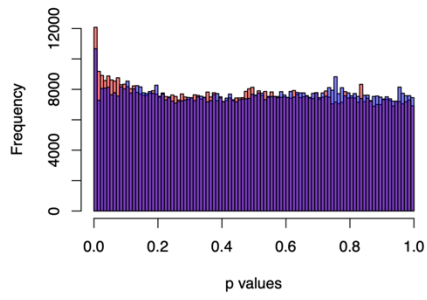
16 autosomal and X-linked purifying selection can be evaluated by comparing the exponential

17 terms in the stationary distributions for X-linked and autosomal loci (*i.e.*: γ_A and γ_X ,

18 respectively). Purifying selection tends to be effectively stronger on the X ($\gamma_A/\gamma_X < 1$) when

19 $N_{eX} > \frac{3}{4}N_{eA}$, and dominance further elaborates on baseline X/autosomal differences

20 attributable to their effective population sizes.



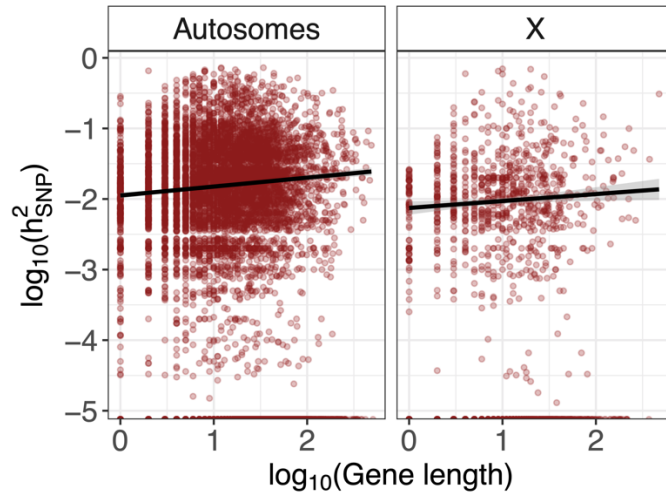
21

22 **Supplementary Figure 3. Histogram of p- and q-values, and quantile-quantile plots,**

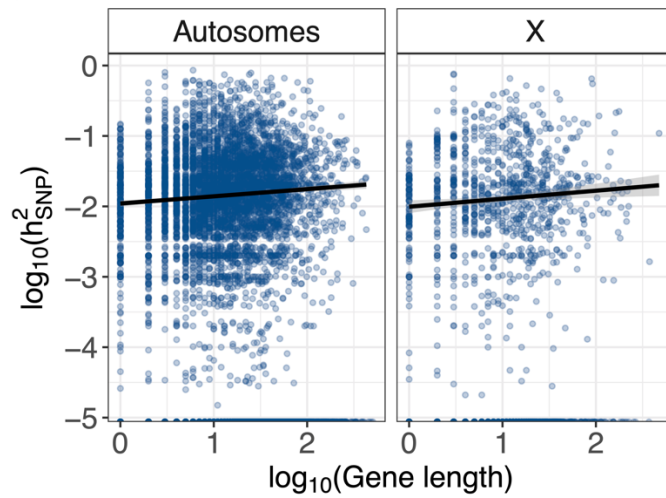
23 **from GWAS of female fitness (red) and male fitness (blue).**

24

Female

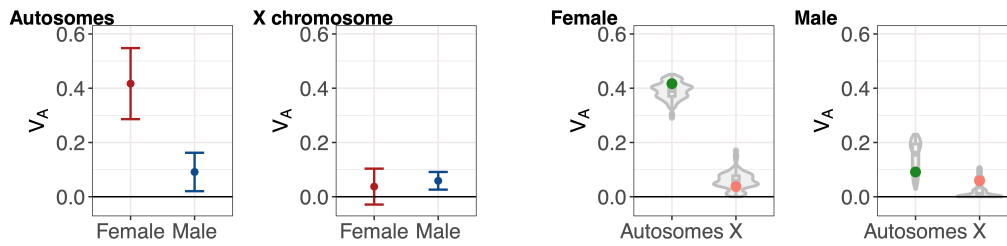
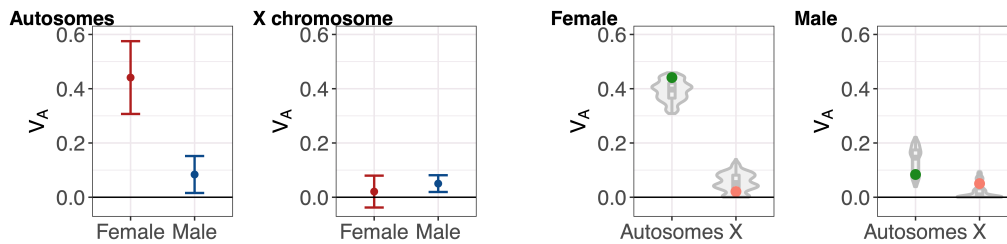


Male



25

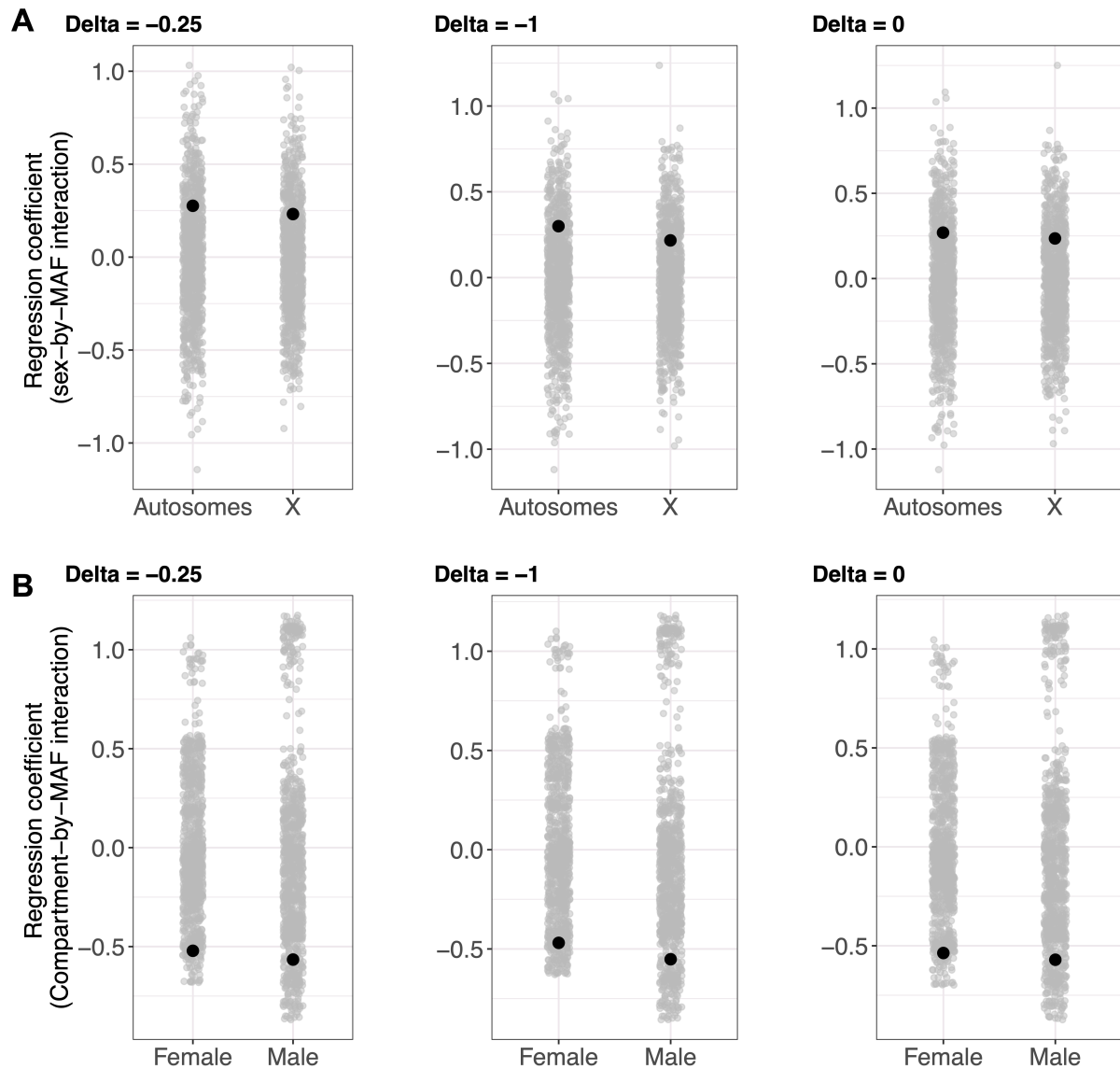
26 **Supplementary Figure 4. Log-log plots of the “length” of a gene (i.e., the number of**
27 **SNPs within a given gene) and its SNP-heritability, for females and males, on autosomes**
28 **and the X, with a line of best fit from a simple linear regression presented for visual**
29 **emphasis.**

delta = -1**delta = 0**

31

32 **Supplementary Figure 5.** Same as Figure 3, presented for two alternative values of δ ,
 33 which is used to scale SNPs by MAF when estimating kinships (see Materials and Methods;
 34 Fig. 4 assumes $\delta = -0.25$). V_A estimates are largely similar across values of δ . Welch t -tests of
 35 the difference between male and female variances yield the following p-values: $p = 0.029$
 36 ($\delta = -1$; autosomes), $p = 0.772$ ($\delta = -1$; X chromosome), $p = 0.018$ ($\delta = 0$; autosomes), $p = 0.658$
 37 ($\delta = 0$; X chromosome). The proportional contribution of the X to total V_A in each sex yields
 38 the following p-values in females ($p = 0.218$, $\delta = -1$; $p = 0.175$, $\delta = 0$) and males ($p = 0.187$, $\delta = -1$;
 39 $p = 0.174$, $\delta = 0$). The ratio of the contributions of the X to total V_A in males vs. females yields
 40 the following p-values: $p = 0.159$ ($\delta = -1$), $p = 0.088$ ($\delta = 0$).

41



42

43 **Supplementary Figure 6. A. Regression coefficients for the sex-by-MAF interaction**

44 **obtained from a GLM of $|\alpha|$ (intercept=female).** Dots denote regression coefficients

45 (black, observed; grey, permuted), presented for different values of δ , which is used to scale

46 SNPs by MAF when estimating kinships (see Materials and Methods). For autosomes,

47 empirical p-values for the sex-by-MAF interaction were as follows: $p=0.287$ ($\delta=-0.25$),

48 $p=0.243$ ($\delta=-1$), $p=0.285$ ($\delta=0$). For the X chromosome, empirical p-values for the sex-by-

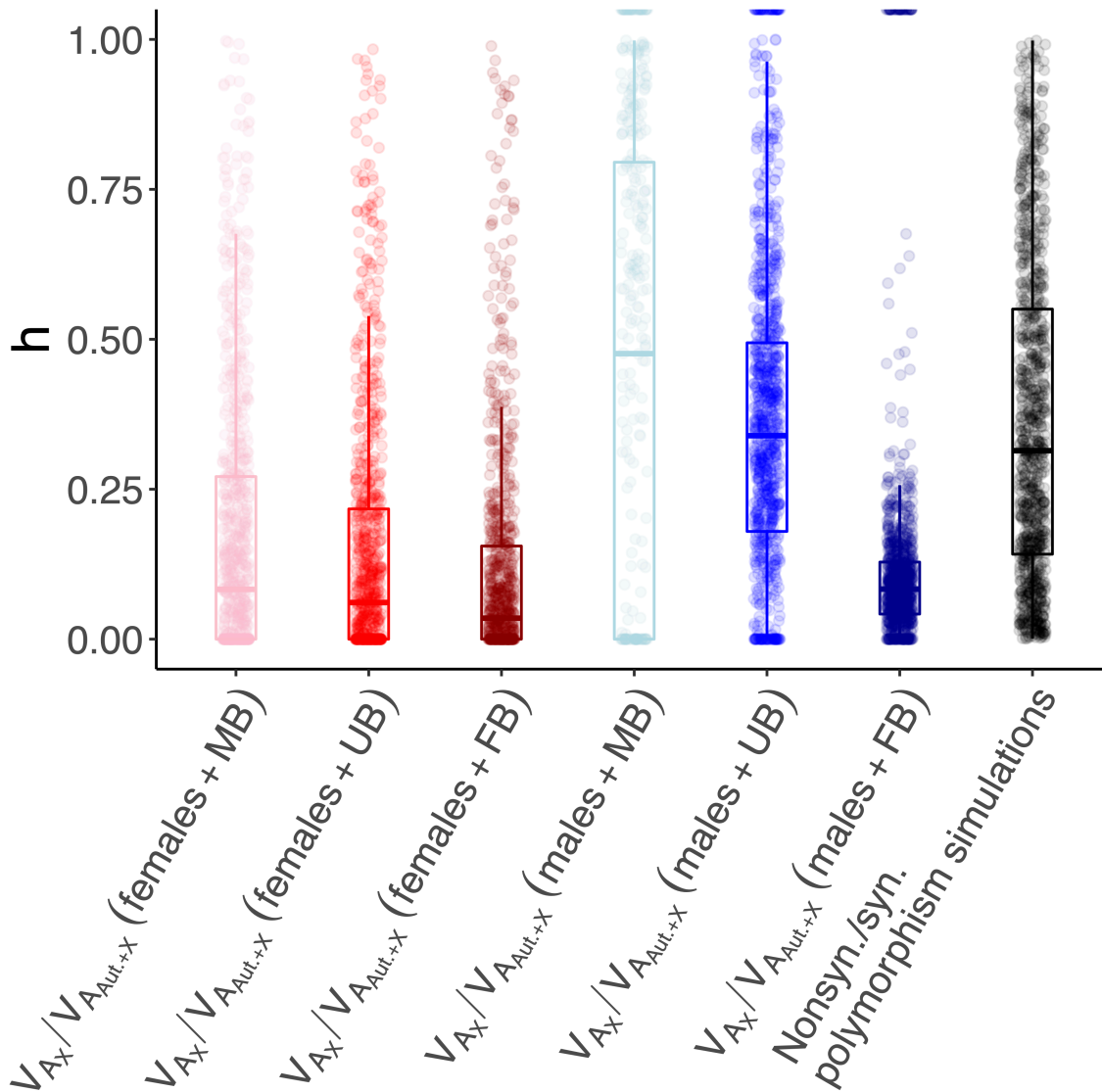
49 MAF interaction were as follows: $p=0.429$ ($\delta=-0.25$), $p=0.457$ ($\delta=-1$), $p=0.430$ ($\delta=0$).

50 **Regression coefficients for the compartment-by-MAF interaction obtained from a GLM**

51 **of $|\alpha|$ (intercept=autosomes).** Dots denote regression coefficients (black, observed; grey,

52 permuted). For females, empirical p-values for the compartment-by-MAF interaction were as
53 follows: $p=0.033$ ($\delta=-0.25$), $p=0.078$ ($\delta=-1$), $p=0.032$ ($\delta=0$). For males, empirical p-values
54 for the compartment-by-MAF interaction were as follows: $p=0.095$ ($\delta=-0.25$), $p=0.105$
55 ($\delta=-1$), $p=0.094$ ($\delta=0$).

56



57

58 **Supplementary Figure 7. Quantitative and population genetic inferences of dominance,**

59 **relaxing the $s_m/s_f=1$ assumption of Fig. 6A.** Boxplots of h estimates, based on quantitative

60 genetic data (the fraction of total V_A that is X-linked in females, left; the fraction of total V_A

61 that is X-linked in males, middle) and population genetic data (coefficients in a logistic

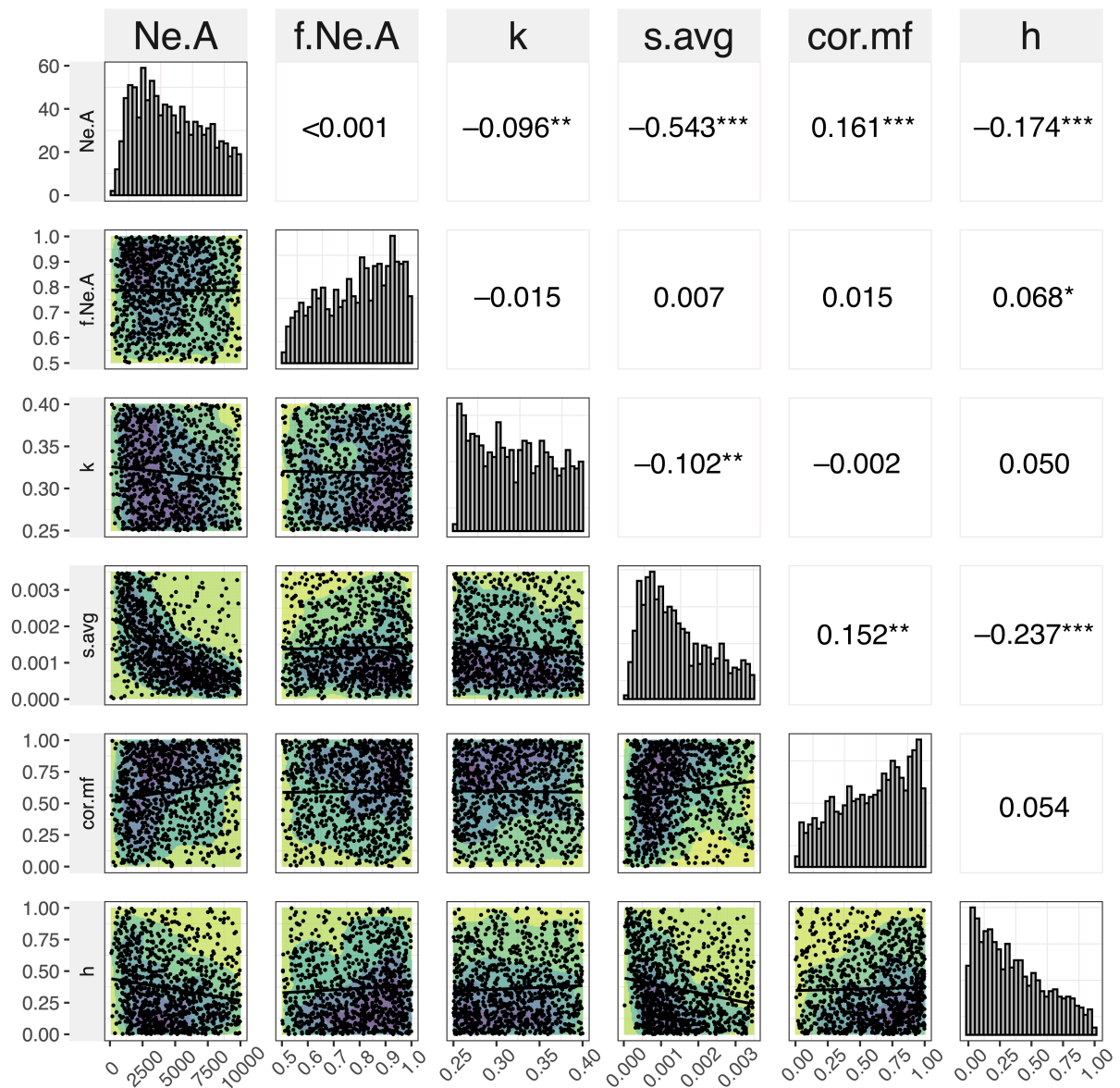
62 regression of nonsynonymous/synonymous status on MAF and chromosome compartment).

63 For visualisation purposes, h estimates greater than one and smaller than zero are not

64 presented. MB denotes $s_m/s_f=2$; UB denotes $s_m/s_f=1$; FB denotes $s_m/s_f=0.5$.

65

66



67

68 **Supplementary Figure 8. Posterior distributions and correlations between evolutionary**

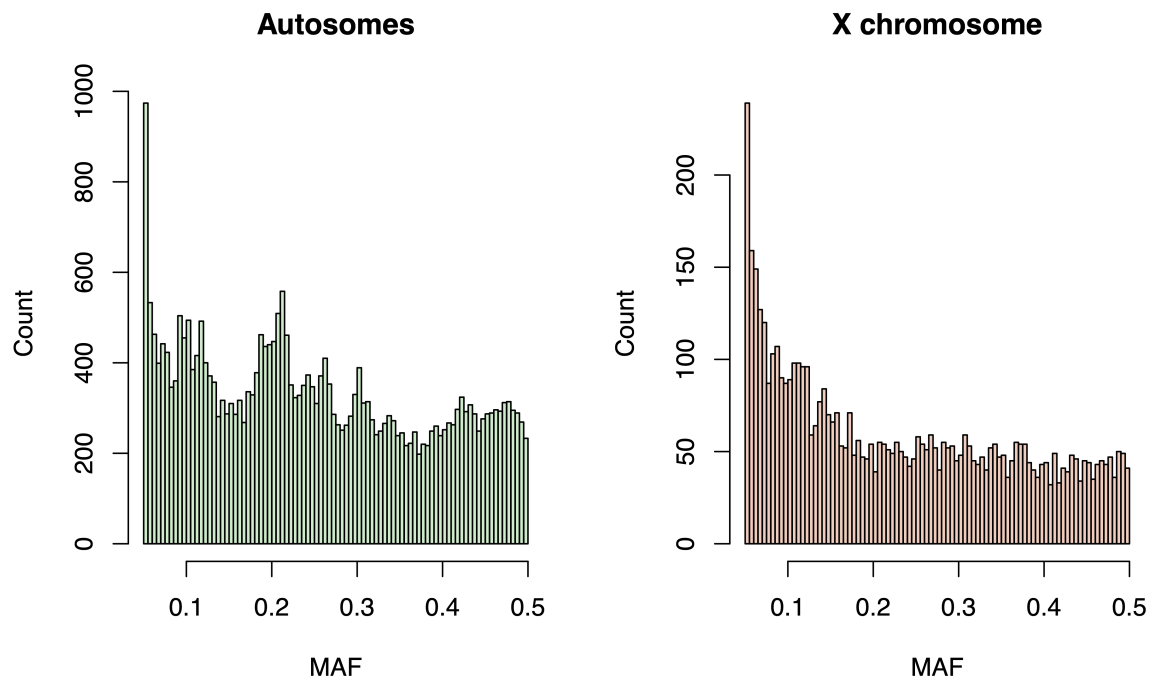
69 **parameters.** Same as Figure 6B, but including the full set of parameters simulated in the

70 Approximate Bayesian Computation approach ($f.Ne.A = N_{eX}/N_{eA} - s.avg = \bar{s} - cor.mf = r$).

71 *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ from Spearman's rank correlations.

72

73



74

75 **Supplementary Figure 9. Allele frequency spectra for LD-pruned autosomal and X-**
76 **linked sites in LH_M .**

77

78

79 **Supplementary Table 1. List of candidate gene IDs (N=70 for females; N=22 for males),**
80 **with p-values from a Likelihood Ratio Test, FDR q-values (maximum q-value=0.3), and**
81 **sex.**

82

Gene_Name	Gene_Symbol	LRT_P_Raw	LRT_q_value	Sex
Prtl99C	FBgn0039707	6.06E-06	0.02414841	Female
Cad99C	FBgn0039709	2.39E-06	0.02414841	Female
RpS8	FBgn0039713	7.30E-06	0.02414841	Female
snoRNA:Me28S-A2564	FBgn0065066	1.13E-05	0.02414841	Female
Zip99C	FBgn0039714	1.02E-05	0.02414841	Female
CG34133	FBgn0083969	7.85E-06	0.02414841	Female
CG31038	FBgn0051038	9.13E-06	0.02414841	Female
Drice	FBgn0019972	1.61E-05	0.02628576	Female
Atg16	FBgn0039705	1.75E-05	0.02628576	Female
CG15514	FBgn0039712	1.46E-05	0.02628576	Female
CG42592	FBgn0260969	2.04E-05	0.02778673	Female
CG15515	FBgn0039719	2.53E-05	0.03159565	Female
CG15517	FBgn0039718	3.94E-05	0.04547063	Female
Rnb	FBgn0039696	5.66E-05	0.06067553	Female
CR31032	FBgn0051032	0.00010917	0.10925006	Female
CG31036	FBgn0051036	0.00011677	0.10955215	Female
dgt1	FBgn0039710	0.00014552	0.12849416	Female
Rrp4	FBgn0034879	0.00016092	0.13419834	Female
neo	FBgn0039704	0.00017979	0.13482607	Female

CG7824	FBgn0039711	0.00018336	0.13482607	Female
Capa	FBgn0039722	0.0001976	0.13482607	Female
CG10802	FBgn0029664	0.00019051	0.13482607	Female
CG10803	FBgn0029666	0.00023591	0.15396717	Female
apt	FBgn0015903	0.00025906	0.16203124	Female
lncRNA:CR44731	FBgn0265944	0.00029142	0.16276372	Female
noc	FBgn0005771	0.00029276	0.16276372	Female
CG34200	FBgn0085229	0.00028904	0.16276372	Female
lncRNA:CR45695	FBgn0267259	0.00033883	0.16953924	Female
scaRNA:PsiU2- 35.45	FBgn0263479	0.00032781	0.16953924	Female
Spg7	FBgn0024992	0.00032318	0.16953924	Female
lncRNA:CR45726	FBgn0267290	0.00039823	0.17903405	Female
lncRNA:CR44126	FBgn0264957	0.00040768	0.17903405	Female
CG42342	FBgn0259244	0.00040875	0.17903405	Female
Gas8	FBgn0029667	0.00041744	0.17903405	Female
lncRNA:CR34335	FBgn0267910	0.00037866	0.17903405	Female
chinmo	FBgn0086758	0.00052025	0.20706549	Female
lncRNA:CR44732	FBgn0265945	0.00055177	0.20706549	Female
lncRNA:CR44730	FBgn0265943	0.00051457	0.20706549	Female
Pi3K59F	FBgn0015277	0.00053136	0.20706549	Female
CG2662	FBgn0024993	0.0005384	0.20706549	Female
Gp210	FBgn0266580	0.00058637	0.20969652	Female
Act42A	FBgn0000043	0.00058672	0.20969652	Female
lncRNA:CR45693	FBgn0267257	0.00061298	0.21398704	Female

CG14270	FBgn0029665	0.00063302	0.21596053	Female
tRNA:Pro-AGG-1-1	FBgn0028882	0.00068841	0.21986644	Female
tRNA:Gly-GCC-1-7	FBgn0011865	0.00067783	0.21986644	Female
Gyc89Db	FBgn0038436	0.00068629	0.21986644	Female
sro	FBgn0262112	0.00076371	0.23883439	Female
wmd	FBgn0034876	0.00081869	0.24096776	Female
levy	FBgn0034877	0.00079521	0.24096776	Female
lncRNA:CR44945	FBgn0266250	0.00080867	0.24096776	Female
lncRNA:CR45303	FBgn0266841	0.00089756	0.25910141	Female
Cpr35B	FBgn0028871	0.00096038	0.27200498	Female
tRNA:Gly-GCC-1-4	FBgn0011862	0.0009941	0.27634139	Female
ed	FBgn0000547	0.0011256	0.27644451	Female
CG15283	FBgn0028844	0.0011184	0.27644451	Female
ZnT41F	FBgn0025693	0.0011273	0.27644451	Female
pita	FBgn0034878	0.0010835	0.27644451	Female
CG10405	FBgn0038431	0.0011179	0.27644451	Female
CG7829	FBgn0039703	0.0010511	0.27644451	Female
trp	FBgn0003861	0.0010501	0.27644451	Female
CG10804	FBgn0029663	0.0011418	0.27644451	Female
Gr59f	FBgn0041234	0.0011667	0.27798942	Female
Gr59e	FBgn0041233	0.001212	0.28427081	Female
lncRNA:CR44856	FBgn0266150	0.001297	0.28807875	Female
CG42680	FBgn0261566	0.0012996	0.28807875	Female
CG43366	FBgn0263109	0.001305	0.28807875	Female
DIP-alpha	FBgn0052791	0.0012518	0.28807875	Female

dpr12	FBgn0085414	0.0013361	0.29066952	Female
Mlc2	FBgn0002773	0.001376	0.29507337	Female
asRNA:CR45830	FBgn0267480	2.80E-05	0.23453937	Male
CG3191	FBgn0023525	3.12E-05	0.23453937	Male
CG32246	FBgn0052246	0.0001453	0.24396407	Male
HDAC1	FBgn0015805	0.00025228	0.24396407	Male
axo	FBgn0262870	0.00026204	0.24396407	Male
Vinc	FBgn0004397	0.00027629	0.24396407	Male
CG14052	FBgn0029606	0.0001953	0.24396407	Male
kz	FBgn0001330	0.00024332	0.24396407	Male
fs(1)K10	FBgn0000810	0.00026701	0.24396407	Male
Or2a	FBgn0023523	0.00015096	0.24396407	Male
CG3091	FBgn0029608	0.00027096	0.24396407	Male
CG3078	FBgn0023524	0.00018535	0.24396407	Male
temp	FBgn0027296	0.00015816	0.24396407	Male
CG3071	FBgn0023527	0.00020196	0.24396407	Male
CG2918	FBgn0023529	0.00024549	0.24396407	Male
Vml	FBgn0085362	0.00019039	0.24396407	Male
CG2865	FBgn0023526	0.00015291	0.24396407	Male
crn	FBgn0000377	0.00029422	0.24536313	Male
Src64B	FBgn0262733	0.0003131	0.24736548	Male
lncRNA:CR45438	FBgn0266987	0.0003672	0.27533586	Male
CG2924	FBgn0023528	0.00040353	0.27533586	Male
PsGEF	FBgn0264598	0.00040295	0.27533586	Male

85 **Supplementary Table 2. Prior and posterior distributions of evolutionary parameters.**

86

Parameter	Prior range	Posterior (2.5%)	Posterior (median)	Posterior (97.5%)
N_{eA}	$10^2, 10^4$	686	4252	9645
N_{eX}/N_{eA}	0.5, 1	0.529	0.805	0.990
k	0.25, 0.4	0.252	0.316	0.396
\bar{s}	$10^{-5}, 3.5 \times 10^{-3}$	1.9×10^{-4}	1.2×10^{-3}	2.2×10^{-3}
r	0, 1	0.050	0.636	0.987
h	0, 1	0.012	0.314	0.914

87

88

89 **Supplementary Text 1. Sex-specific contributions of the X to the additive genetic**
 90 **variance under mutation-selection balance.**

91 In females, the X-linked and autosomal additive genetic variances are given by:

$$92 \quad V_{A,f}^X = \sum_{i=1}^{n_X} 2p_i q_i (s_{f,i} h_i + s_{f,i} q_i (1 - 2h_i))^2 \approx \sum_{i=1}^{n_X} \frac{6u_i s_{f,i} h_i^2}{2h_i + s_{m,i}/s_{f,i}}$$

$$93 \quad V_{A,f}^{aut.} = \sum_{i=1}^{n_A} 2p_i q_i (s_{f,i} h_i + s_{f,i} q_i (1 - 2h_i))^2 \approx \sum_{i=1}^{n_A} \frac{4u_i s_{f,i} h_i}{1 + s_{m,i}/s_{f,i}}$$

94 where n_X and n_A represent the number of X-linked and autosomal loci at mutation-selection
 95 equilibrium. The final approximation is based on mutation-selection balance theory and the
 96 approximation is to first order in the mutation rate for each locus.

97 In males, the X-linked and autosomal additive genetic variances are given by:

$$98 \quad V_{A,m}^X = \sum_{i=1}^{n_X} p_i q_i s_{m,i}^2 \approx \sum_{i=1}^{n_X} \frac{3u_i s_{m,i}}{1 + 2h_i s_{f,i}/s_{m,i}}$$

$$99 \quad V_{A,m}^{aut.} = \sum_{i=1}^{n_A} 2p_i q_i (s_{m,i} h_i + s_{m,i} q_i (1 - 2h_i))^2 \approx \sum_{i=1}^{n_A} \frac{4u_i s_{m,i} h_i}{1 + s_{f,i}/s_{m,i}}$$

100 To approximate dominance compatible with X-linked and autosomal variances, we assume
 101 that h_i and $s_{m,i}/s_{f,i}$ are constant across loci, and that u_i , $s_{f,i}$, and $s_{m,i}$ have the same distribution
 102 across X-linked and autosomal loci. Under these assumptions, we have:

$$103 \quad V_{A,f}^X \approx \frac{6h^2}{2h + s_m/s_f} \sum_{i=1}^{n_X} u_i s_{f,i} \approx \frac{6h^2}{2h + s_m/s_f} n_X E[u_i s_{f,i}]$$

$$104 \quad V_{A,f}^{aut.} \approx \frac{4h}{1 + s_m/s_f} \sum_{i=1}^{n_A} u_i s_{f,i} \approx \frac{4h}{1 + s_m/s_f} n_A E[u_i s_{f,i}]$$

$$105 \quad V_{A,m}^X \approx \frac{3}{1 + 2h s_f/s_m} \sum_{i=1}^{n_X} u_i s_{m,i} \approx \frac{3}{1 + 2h s_f/s_m} n_X E[u_i s_{m,i}]$$

106
$$V_{A,m}^{aut.} \approx \frac{4h}{1 + s_f/s_m} \sum_{i=1}^{n_A} u_i s_{m,i} \approx \frac{4h}{1 + s_f/s_m} n_A E[u_i s_{m,i}]$$

107 Using the above approximations, the contribution of the X to the additive genetic variance in
 108 females and males (respectively) will be:

109
$$F_X = \frac{V_{A,f}^X}{V_{A,f}^X + V_{A,f}^{aut.}} \approx \frac{3hP_X}{3hP_X + 2(1 - P_X) \frac{2h + s_m/s_f}{1 + s_m/s_f}}$$

110
$$M_X = \frac{V_{A,m}^X}{V_{A,m}^X + V_{A,m}^{aut.}} \approx \frac{3P_X}{3P_X + 4h(1 - P_X) \frac{1 + 2h s_f/s_m}{1 + s_f/s_m}}$$

111 where P_X represents the fraction of the haploid genome that is X-linked (e.g., ~20% in *D.*
 112 *melanogaster*). Solving for h , we obtain the dominance coefficient consistent with F_X :

113
$$h \approx \frac{2 s_m/s_f}{3(1 + s_m/s_f) \frac{P_X(1 - F_X)}{F_X(1 - P_X)} - 4}$$

114 and the dominance coefficient consistent with M_X :

115
$$h = \frac{s_m}{4s_f} \sqrt{1 + \frac{6s_f}{s_m} \left(1 + \frac{s_f}{s_m}\right) \frac{P_X(1 - M_X)}{M_X(1 - P_X)}} - \frac{s_m}{4s_f}$$