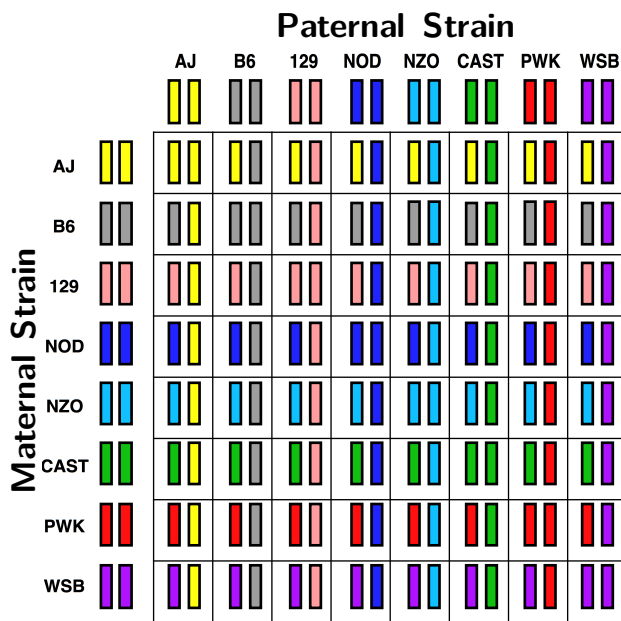


## SUPPLEMENTAL FIGURES AND TABLES

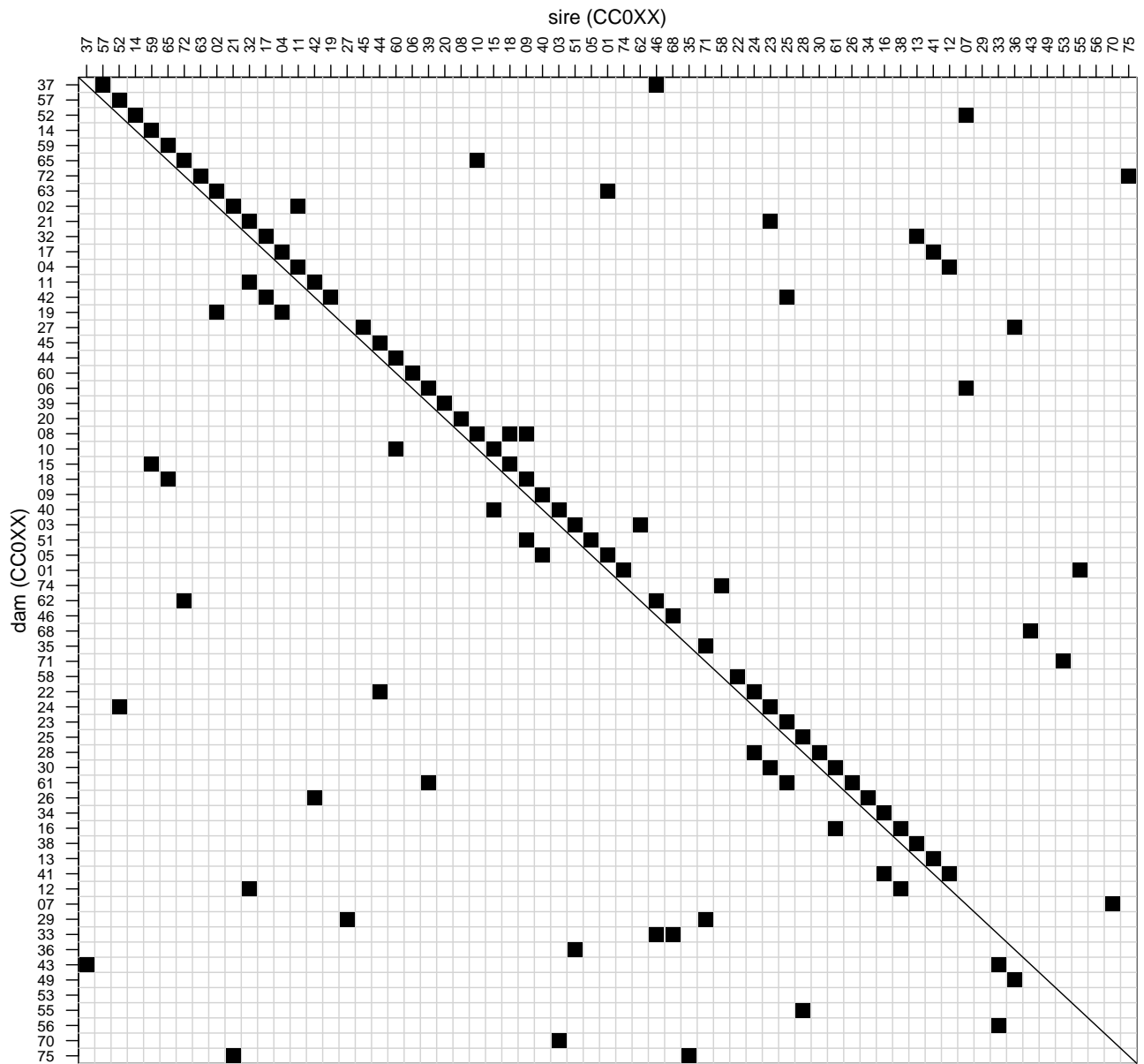
**A**



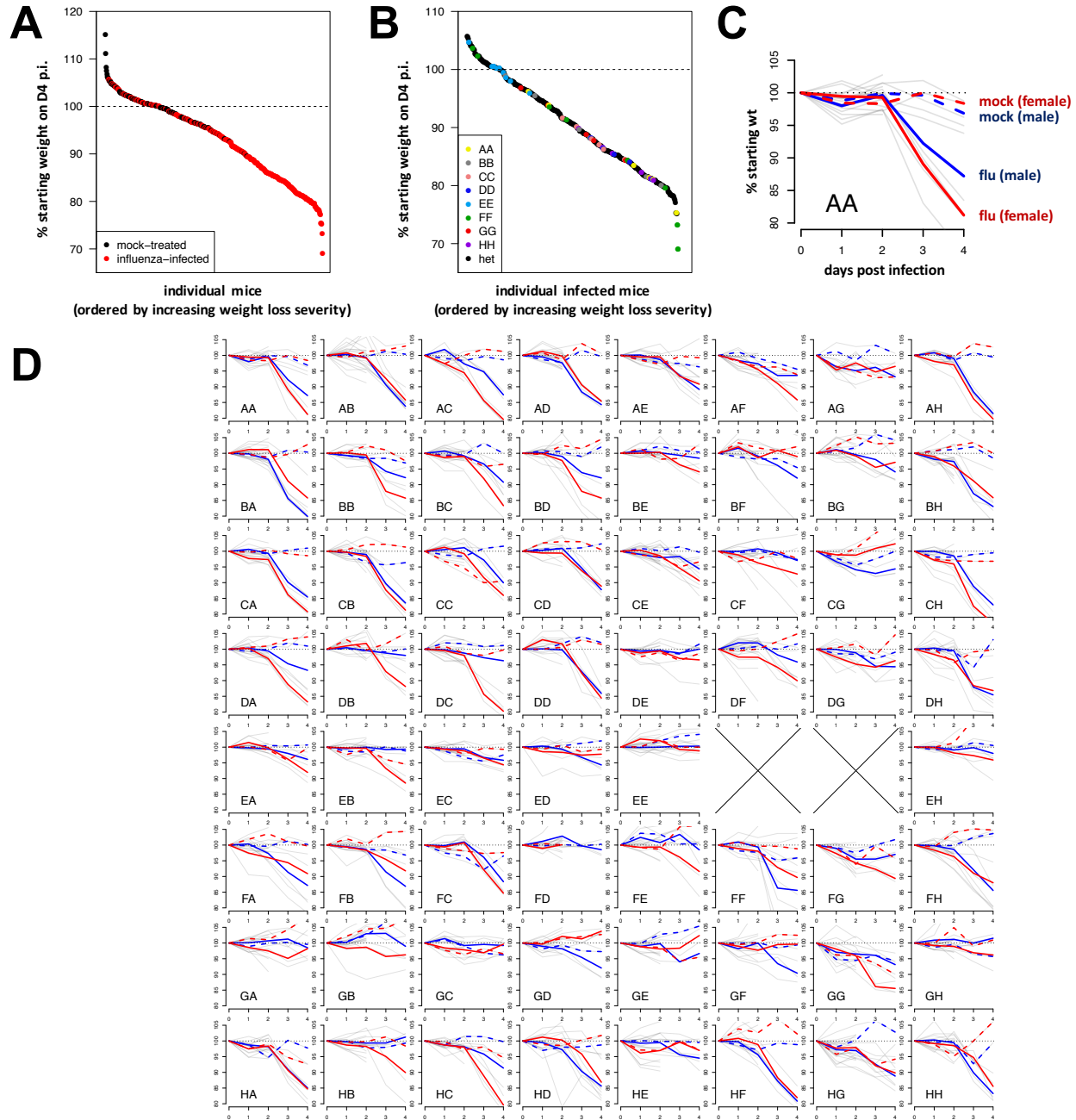
**B**

		sire							
		AJ	B6	129	NOD	NZO	CAST	PWK	WSB
dam	mock								
	flu								
	AJ	5 / 12	6 / 18	4 / 12	5 / 15	5 / 15	4 / 12	4 / 12	4 / 12
	B6	5 / 15	4 / 11	5 / 15	4 / 12	4 / 12	4 / 12	4 / 12	5 / 15
	129	4 / 12	4 / 12	4 / 11	4 / 12	6 / 18	4 / 12	4 / 11	4 / 12
	NOD	4 / 12	4 / 11	5 / 15	4 / 11	4 / 12	5 / 16	4 / 12	4 / 12
	NZO	4 / 12	4 / 12	4 / 12	4 / 12	5 / 15	-	-	4 / 10
	CAST	4 / 11	4 / 11	4 / 11	4 / 11	4 / 12	4 / 10	4 / 10	5 / 14
	PWK	4 / 12	4 / 12	4 / 12	4 / 12	5 / 11	4 / 12	4 / 11	5 / 14
WSB	4 / 12	4 / 12	4 / 12	5 / 14	4 / 12	4 / 11	6 / 17	5 / 13	

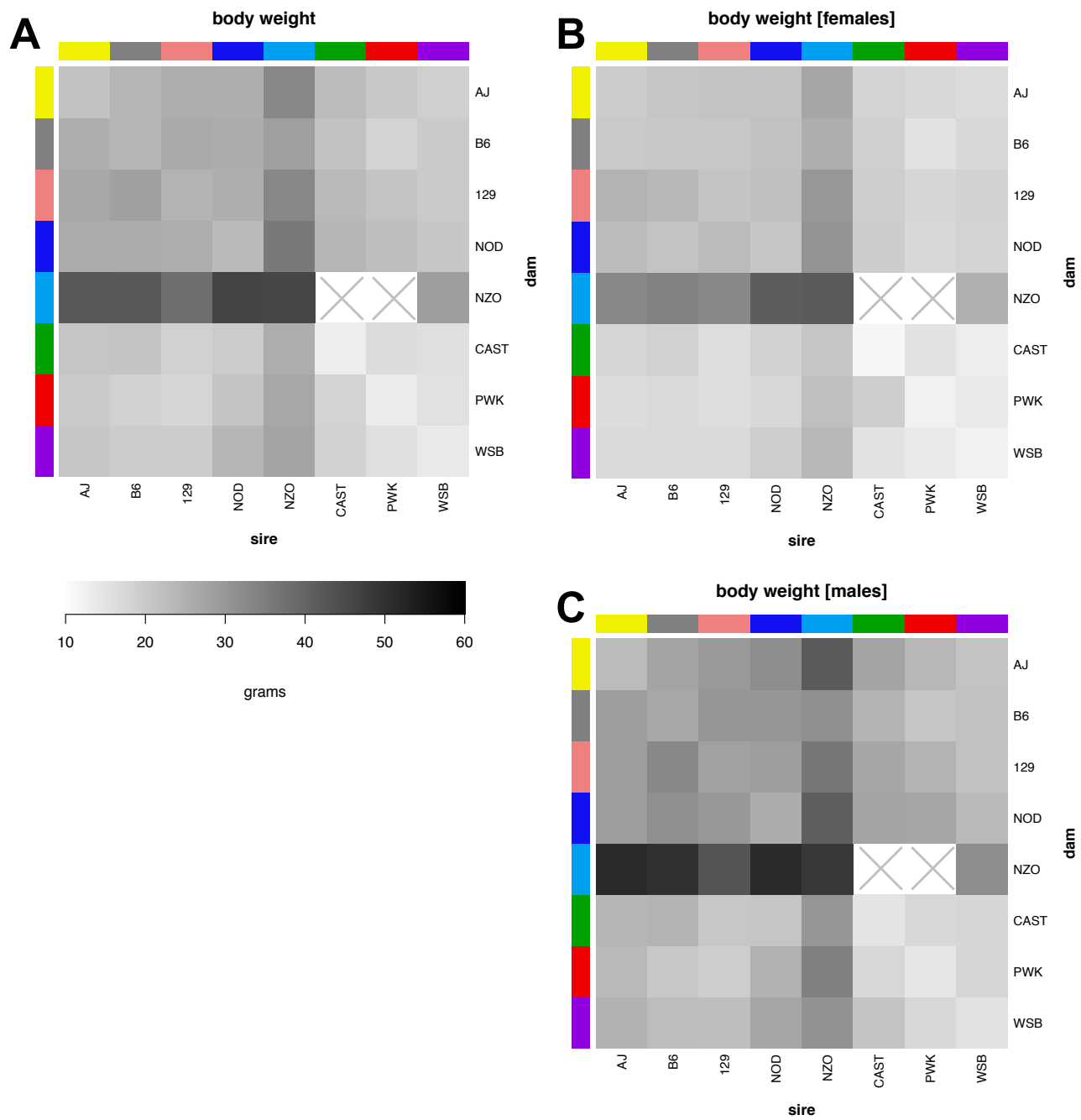
**Figure S1** Diallel crossing design for the influenza diallel experiment. (A) Eight inbred *Mus musculus* strains were crossed in both directions to generate animals used in this experiment. All of the animals were followed from D0 through D2. Approximately half of the animals were followed through D4, and the remaining half of the mice were sacrificed on D2 (for analysis not included in this manuscript). (B) Of the 1,043 mice in this experiment, 268 received mock treatment, and 775 received influenza (flu) inoculation, or approximately 1 mock for every 2.9 infected mice within each category. There were one hundred twenty-nine inbred mice and 914 heterozygous (hybrid F1) mice used in this study. Crosses that were not observed (marked with a "-") include NZO×CAST and NZO×PWK, for which viable offspring cannot be produced.



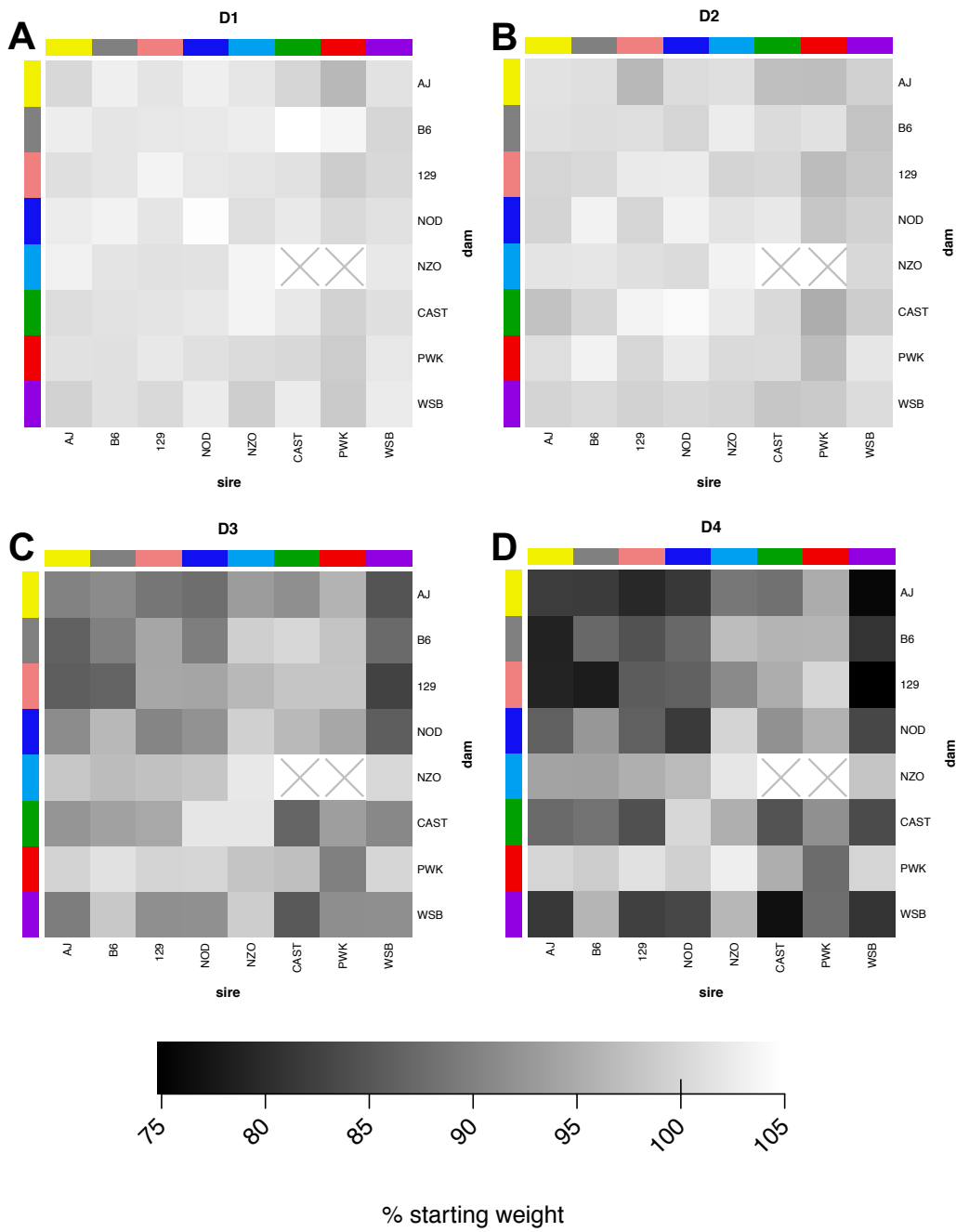
**Figure S2** CC-RIX crossing design for the influenza infection experiment. As part of a larger CC-RIX QTL mapping experiment, 65 Collaborative Cross (CC) RI strains were crossed, approximately once as dam and once as sire in a round robin breeding scheme, to generate female animals in 105 CC-RIX lines, aged 8-12 weeks, that were sacrificed on day 7 (D7) post-infection, and used in this experiment. Weights for all of the animals were measured from D0 through D7. There were 1,402 heterozygous (hybrid F1) mice used in this study.



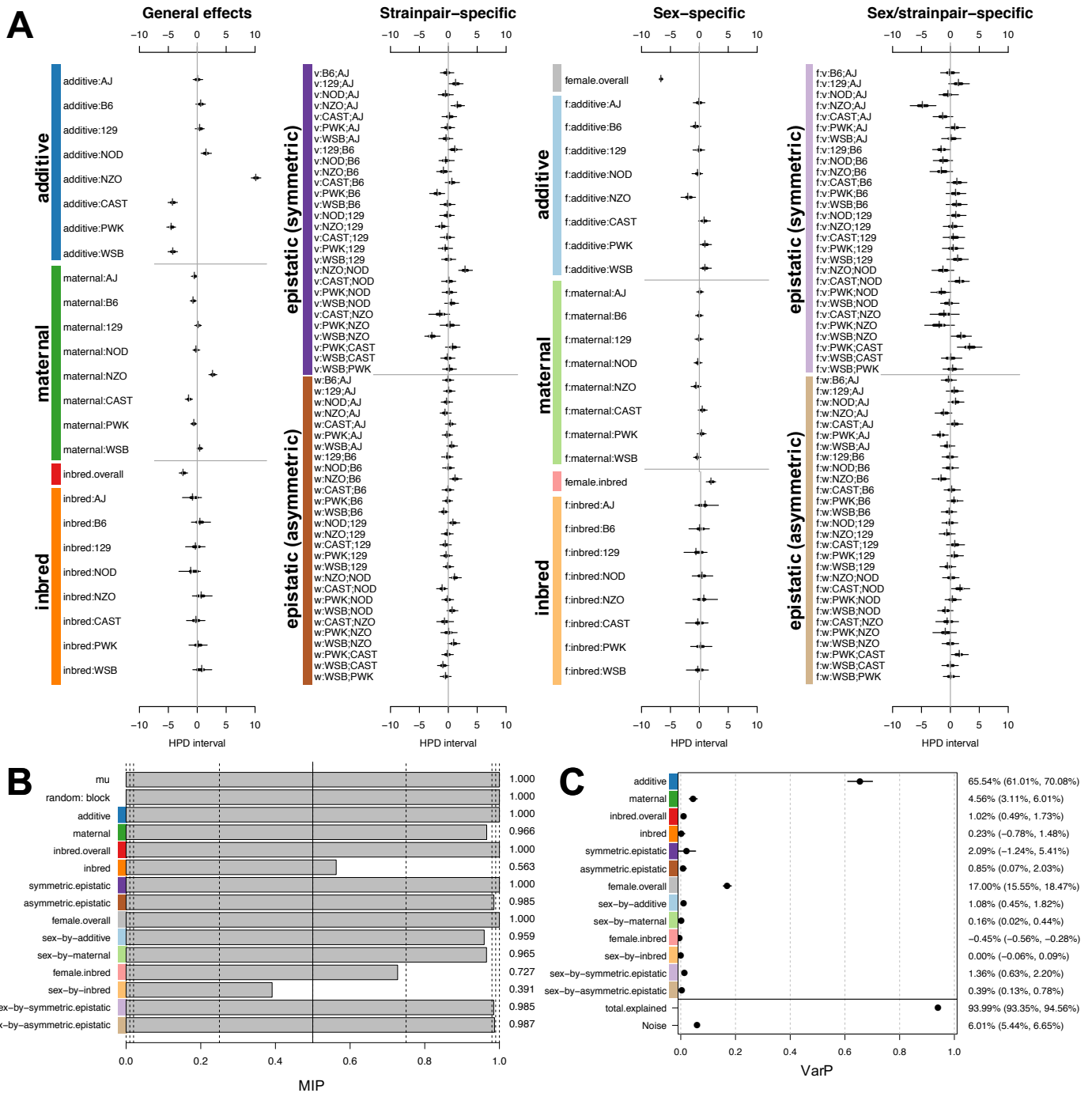
**Figure S3** The raw distribution and timecourse of mock- and flu-induced weight change in the diallel. (A) Rank-ordered distribution of individual mock- and flu-induced percent weight change of inbred and F1 animals at D4 p.i. (B) Rank-ordered distribution of inbred and F1 flu-infected percent weight change at D4 p.i. (C) An example of raw weight change curves for AA (AJ x AJ) male and female mice. (D) The panel of raw weights for the 62 possible diallel categories. In (C) and (D), y-axes indicate percent of D0 weight, and x-axes indicate day(s) post-infection, while grey lines indicate individual weight change trajectories; colored lines indicate mean male (blue) and mean female (red) weight trajectories, and among these means, colored line styles indicate mock (dashed) and influenza (solid) treatment means within each group. In (D), the large X's in EF and EG indicate non-productive F1 matings. Inbred mouse lines AJ, B6, 129, NOD, NZO, CAST, PWK, and WSB are indicated by letters A through H, respectively, with the first letter indicating maternal parentage and the second letter indicating paternal parentage.



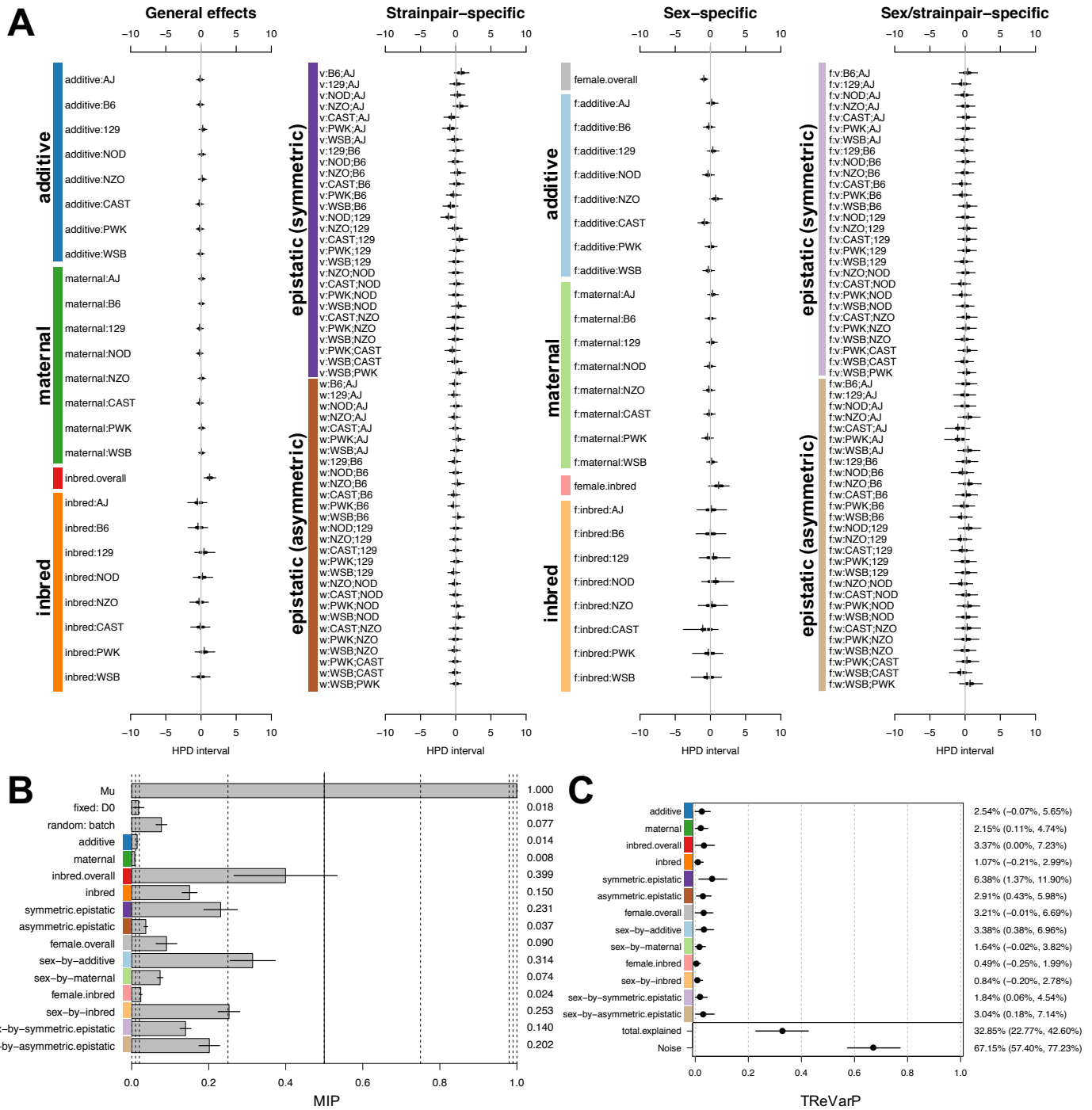
**Figure S4** Body mass in a diallel cross of inbred mice. (A) Baseline body weight (in grams) for (B) male and (C) female 8-12 week old mice (n=1,043), presented as mean values across 62 inbred and F1 diallel categories.



**Figure S5** Weight loss in influenza-infected mice from a diallel cross of inbred mice. (A) Change in body weight on (A) day 1 (D1), (B) D2, (C) D3, and (D) D4 post-infection, presented as mean values of percent starting weight across 62 inbred and F1 diallel categories.

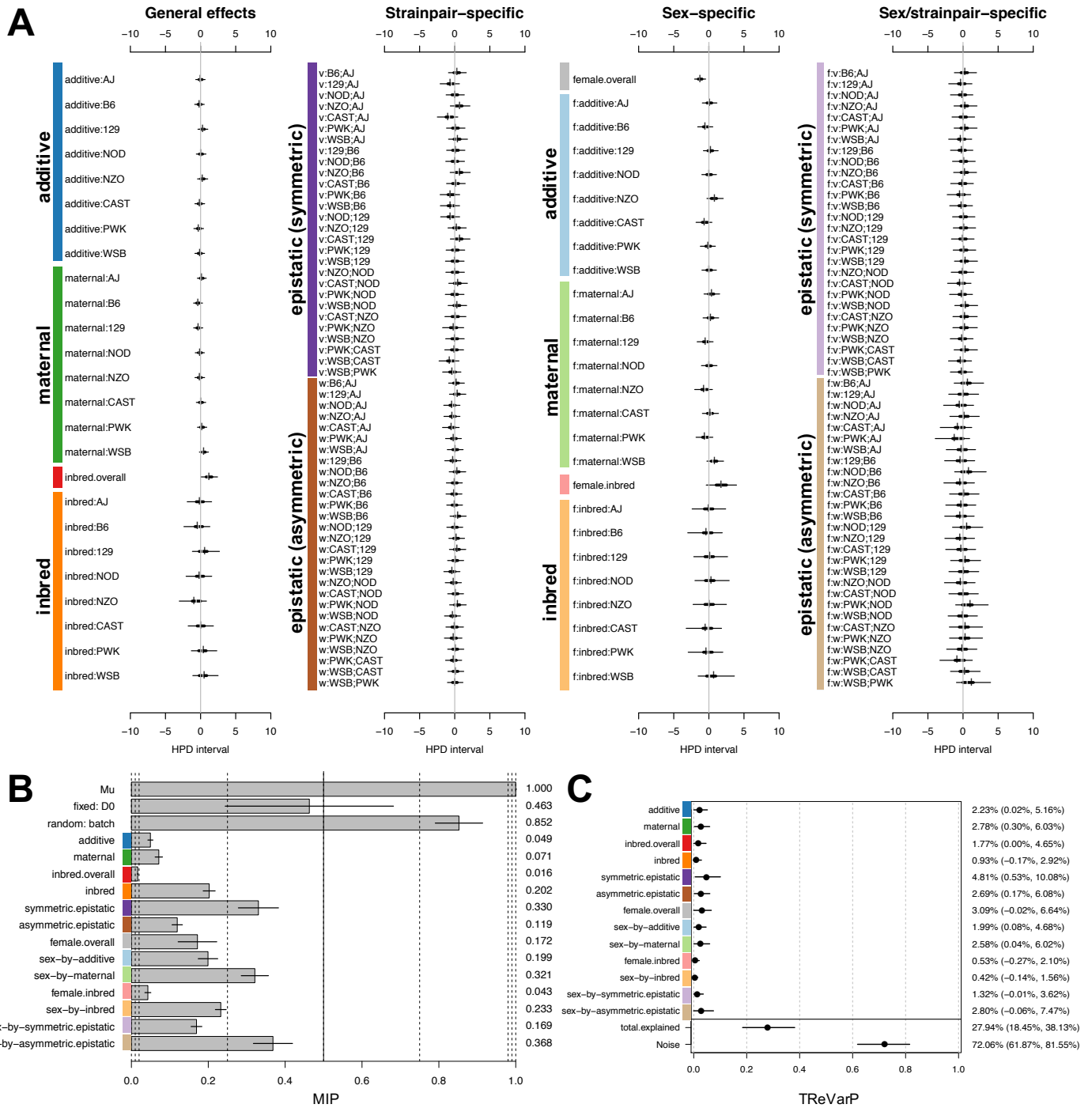


**Figure S6** Diallel effects on D0 body weight in a diallel cross of inbred mice. (A) Effect estimates for additive, maternal, inbred, and epistatic effects, including sex-specific effects, are presented as highest posterior density intervals (in grams) for adult baseline body weight in 8-12 week old mice ( $n=1,043$ ). Parameters are labeled according to the methods, and intervals are presented as in Figure 4A. Symmetric epistatic, asymmetric epistatic, and sex-specific parameters are indicated by “v.”, “w.”, and “f.”, respectively. The overall mean,  $\mu$ , (not shown) is 23.97 (23.56, 24.41) grams. (B) Posterior mean model inclusion probabilities (MIPs) are given for effect parameter classes. (C) Variance projection (VarPs), a generalization of heritability to the diallel effects classes, are shown for three overall effects, five random effects classes, and five corresponding sex-specific random effects classes (with posterior median and 95% HPDs).

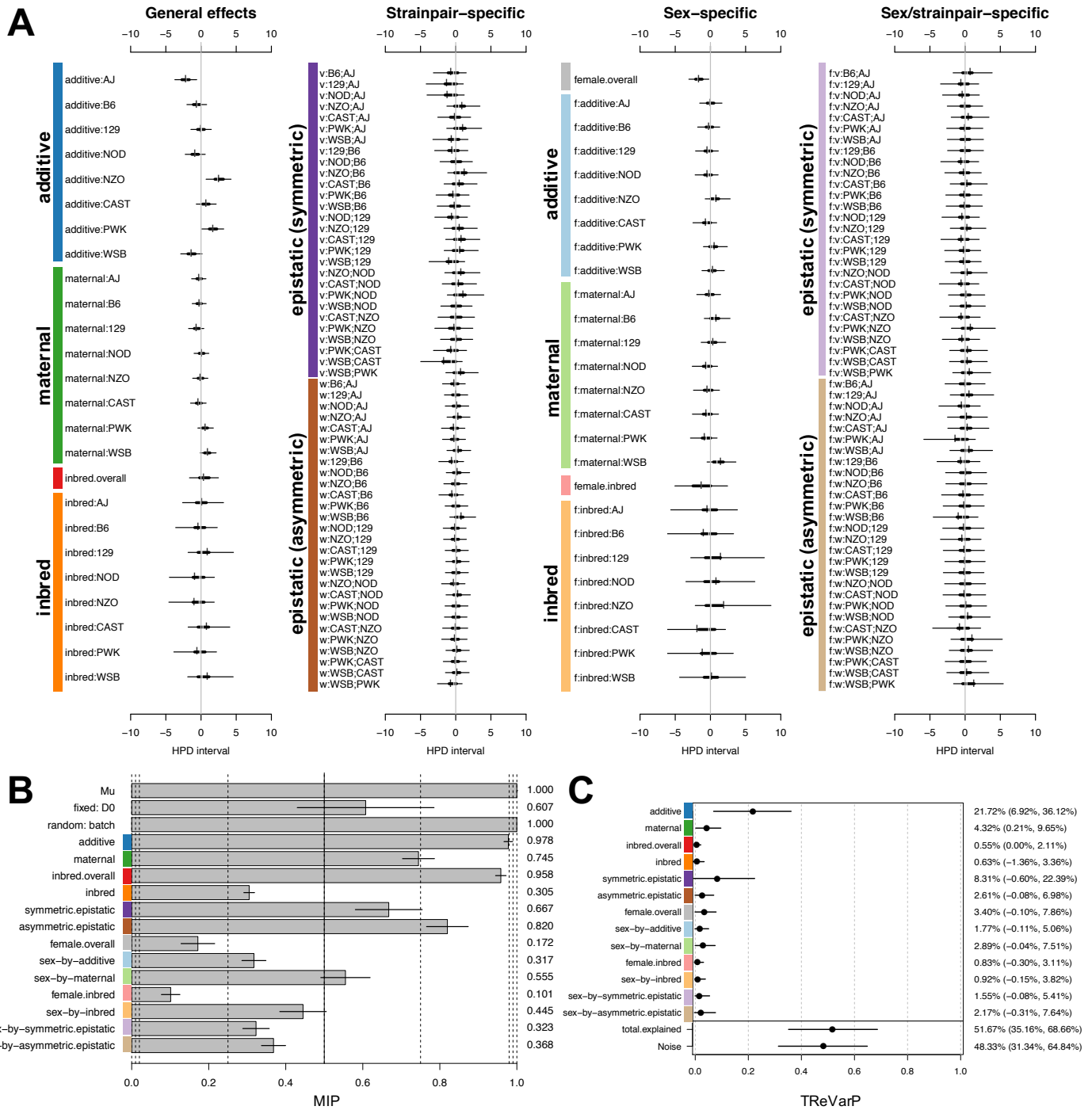


**Figure S7** Diallel effects on host infection response (weight change) at D1 post-infection, using multiple imputation matched quartets. Effect estimates for additive, maternal, inbred, and epistatic effects, including sex-specific effects, are presented as highest posterior density intervals (in percent starting weight) in 8-12 week old mice ( $n=1,042$ ). Parameters are labeled according to the methods, and intervals are presented as in Figure 4A. Symmetric epistatic, asymmetric epistatic, and sex-specific parameters are indicated by "v:", "w:", and "f:", respectively. The overall treatment effect  $\theta$  is  $-0.131\%$  ( $-0.484\%, 0.223\%$ ). (B) Model inclusion probabilities (MIPs) are given (posterior mean  $\pm$  1 s.d.) for effect parameter classes. (C) Treatment response variance projections (TReVarPs), a generalization of heritability to the diallel effects classes, are shown for three overall effects, five random effects classes, and five corresponding sex-specific random effects classes (with posterior median and 95% HPDs).

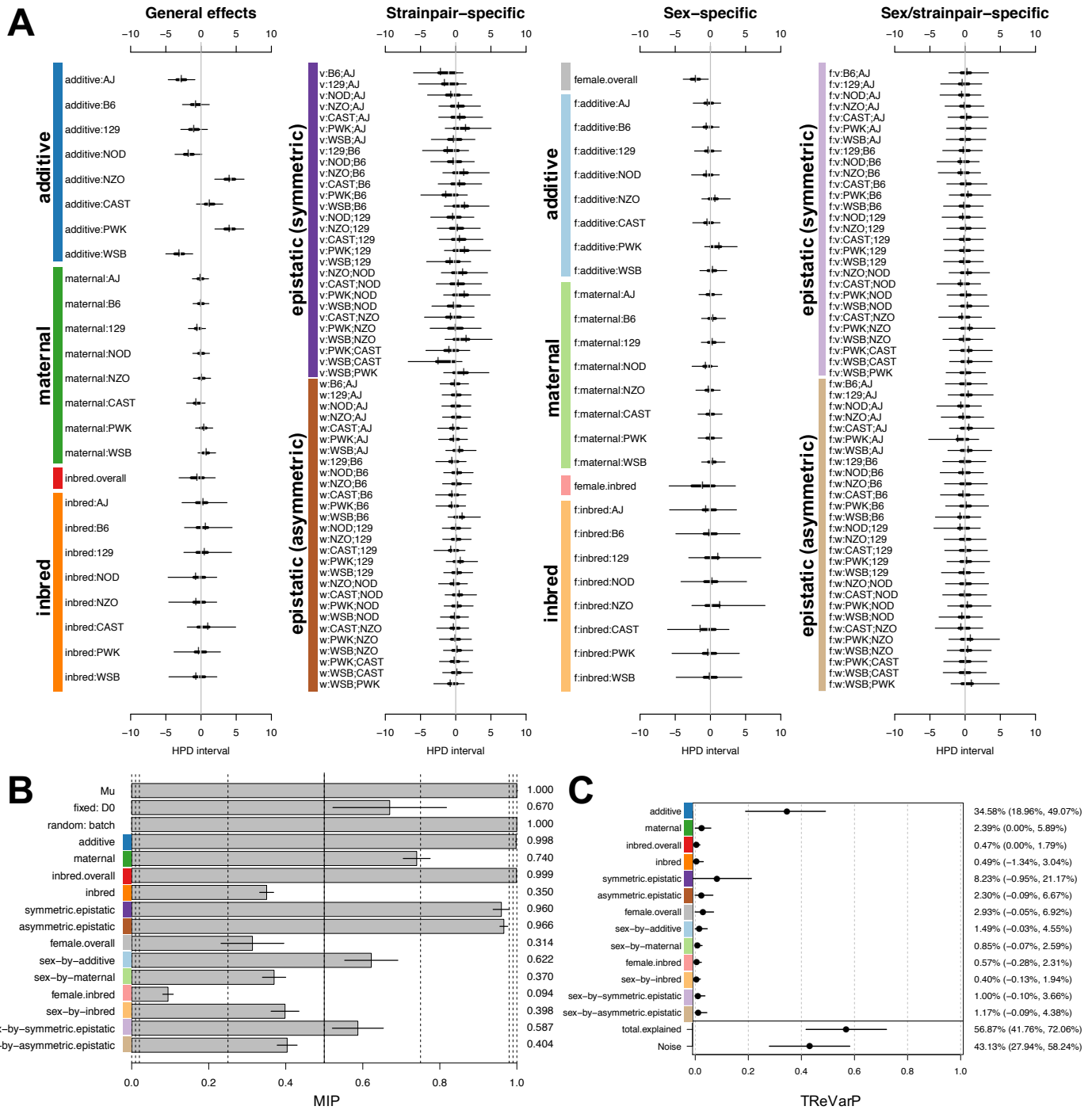




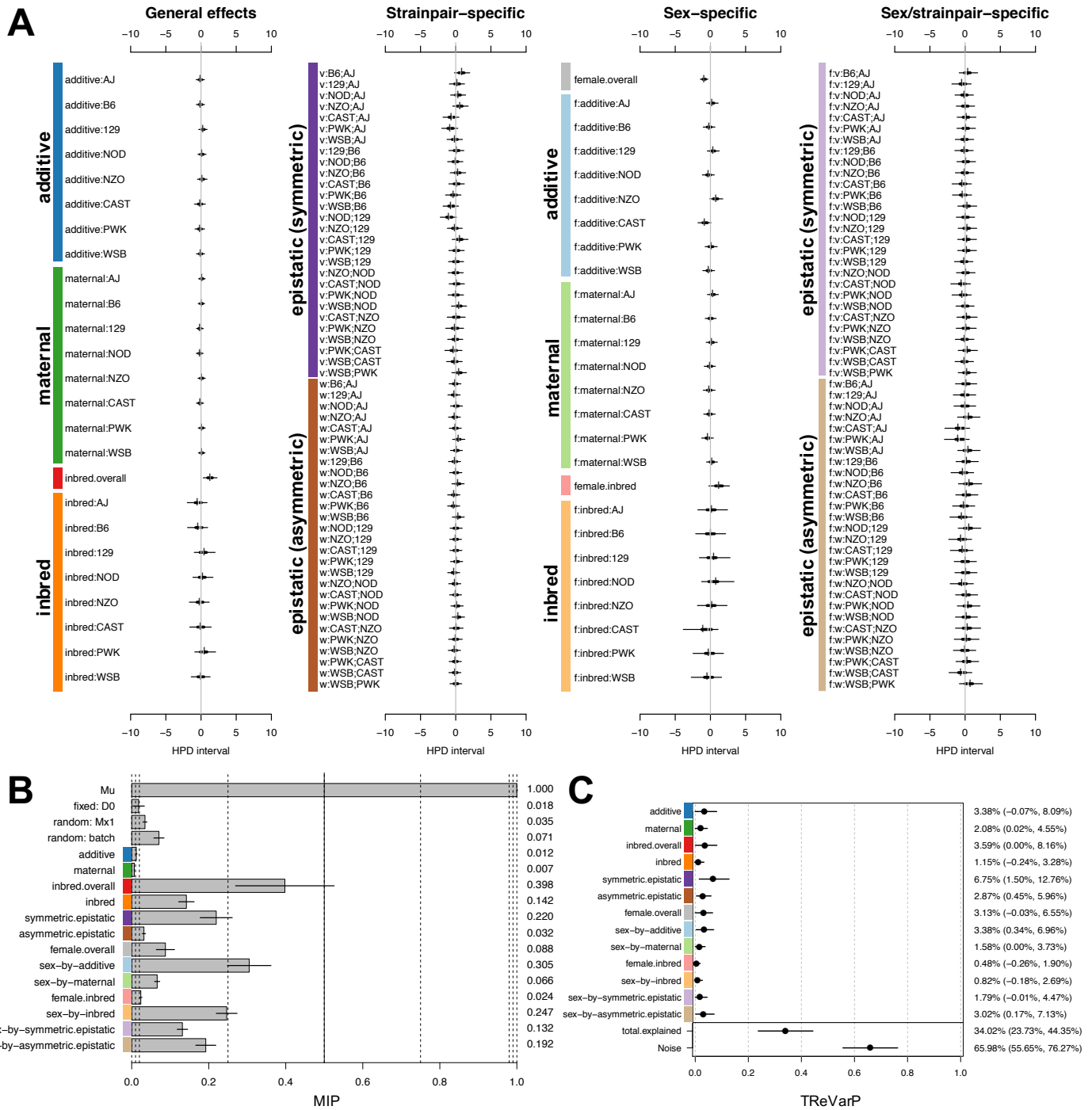
**Figure S8** Diallel effects on host infection response (weight change) at D2 post-infection, using multiple imputation quartets. Effect estimates for additive, maternal, inbred, and epistatic effects, including sex-specific effects, are presented as highest posterior density intervals (in percent starting weight) in 8-12 week old mice ( $n=1,042$ ). Parameters are labeled according to the methods, and intervals are presented as in Figure 4A. Symmetric epistatic, asymmetric epistatic, and sex-specific parameters are indicated by “v:”, “w:”, and “f:”, respectively. The overall treatment effect  $\theta$  is  $-0.833\%$  ( $-1.328\%$ ,  $-0.318\%$ ). (B) Model inclusion probabilities (MIPs) are given (posterior mean  $\pm$  1 s.d.) for effect parameter classes. (C) Treatment response variance projections (TReVarPs), a generalization of heritability to the diallel effects classes, are shown for three overall effects, five random effects classes, and five corresponding sex-specific random effects classes (with posterior median and 95% HPDs).



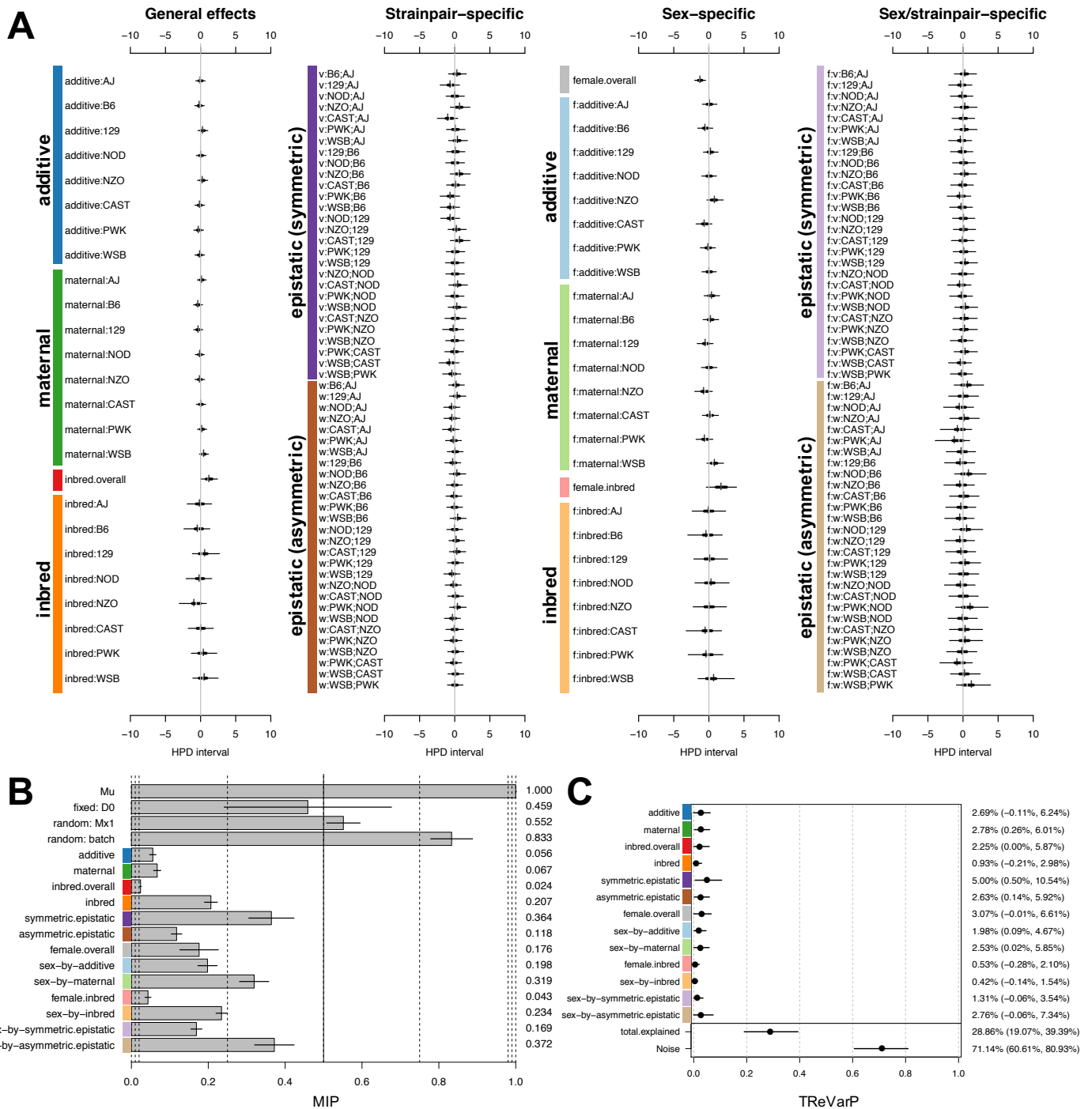
**Figure S9** Diallel effects on host infection response (weight change) at D3 post-infection, using multiple imputation quartets. Effect estimates for additive, maternal, inbred, and epistatic effects, including sex-specific effects, are presented as highest posterior density intervals (in percent starting weight) in 8-12 week old mice ( $n=514$ ). Parameters are labeled according to the methods, and intervals are presented as in Figure 4A. Symmetric epistatic, asymmetric epistatic, and sex-specific parameters are indicated by "v:", "w:", and "f:", respectively. The overall treatment effect  $\theta$  is -5.594% (-6.470%, -4.729%). (B) Model inclusion probabilities (MIPs) are given (posterior mean  $\pm$  1 s.d.) for effect parameter classes. (C) Treatment response variance projections (TRVarPs), a generalization of heritability to the diallel effects classes, are shown for three overall effects, five random effects classes, and five corresponding sex-specific random effects classes (with posterior median and 95% HPDs).



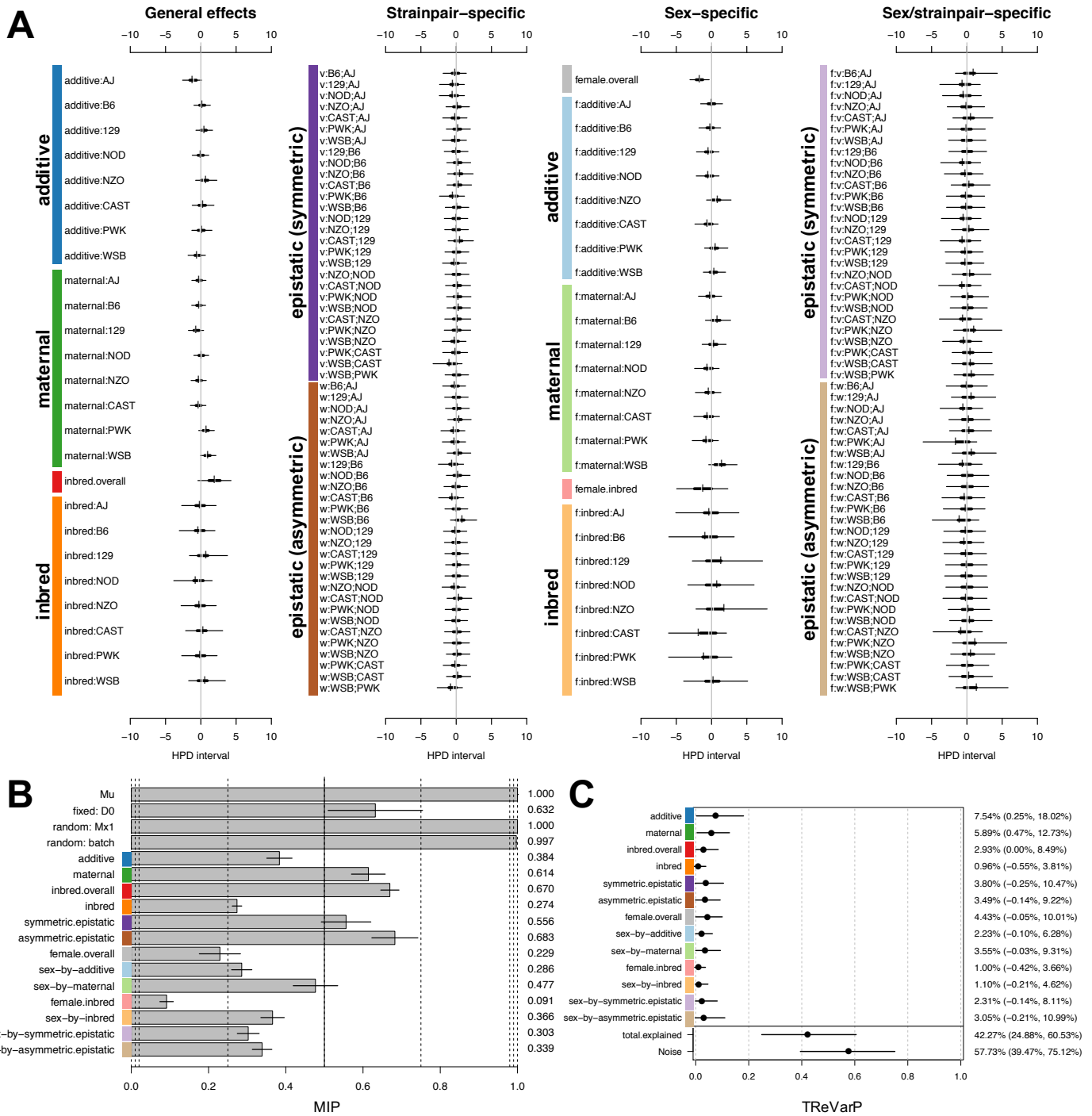
**Figure S10** Diallel effects on host infection response (weight change) at D4 post-infection, using multiple imputation matched quartets. Effect estimates for additive, maternal, inbred, and epistatic effects, including sex-specific effects, are presented as highest posterior density intervals (in percent starting weight) in 8-12 week old mice ( $n=513$ ). Parameters are labeled according to the methods, and intervals are presented as in Figure 4A. Symmetric epistatic, asymmetric epistatic, and sex-specific parameters are indicated by "v:", "w:", and "f:", respectively. The overall treatment effect  $\theta$  is -8.849% (-9.920%, -7.779%). (B) Model inclusion probabilities (MIPs) are given (posterior mean  $\pm$  1 s.d.) for effect parameter classes. (C) Treatment response variance projections (TRVarPs), a generalization of heritability to the diallel effects classes, are shown for three overall effects, five random effects classes, and five corresponding sex-specific random effects classes (with posterior median and 95% HPDs).



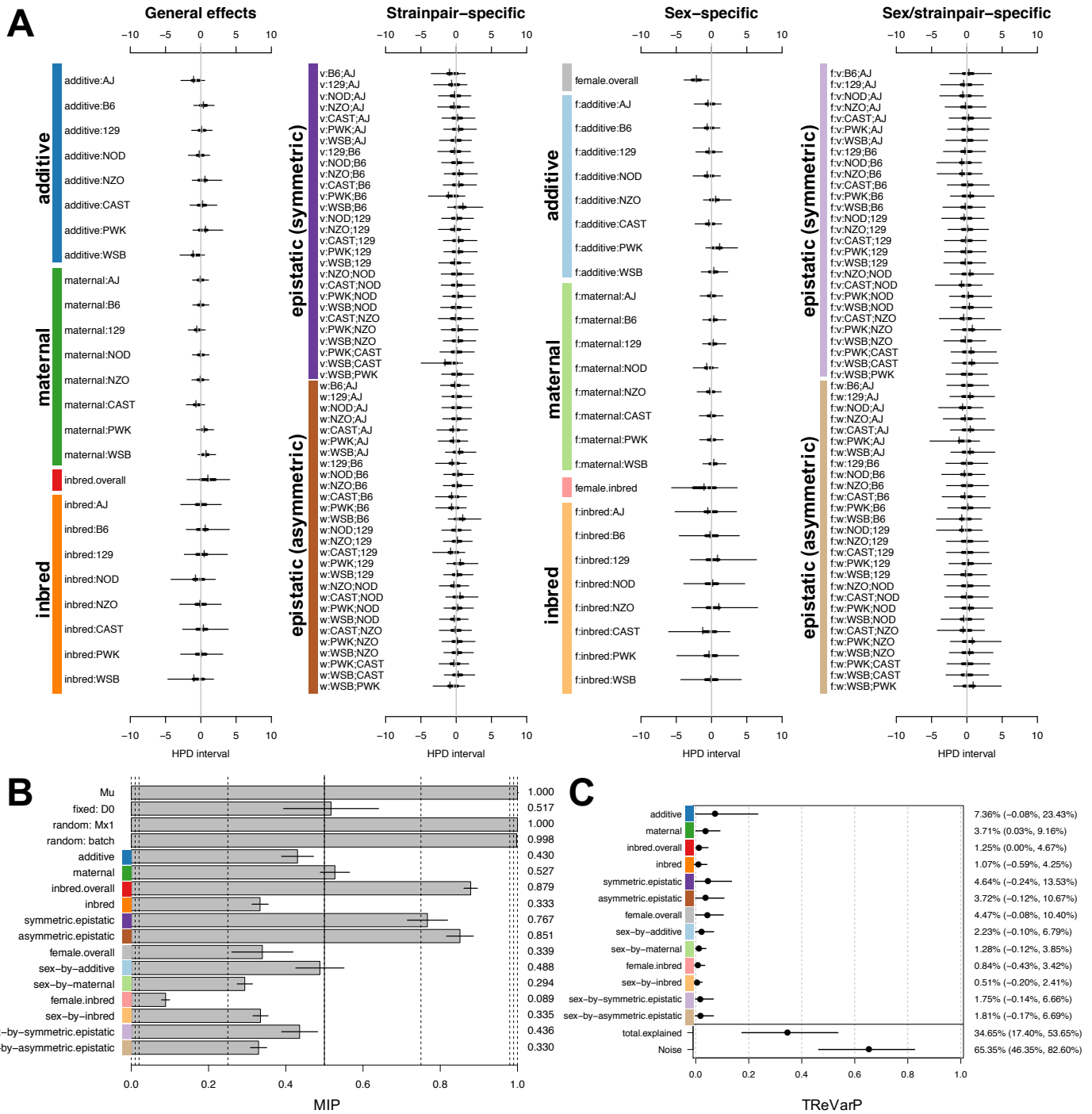
**Figure S11** Diallel effects on host infection response (weight change) at D1 post-infection, using multiple imputation matched quartets and accounting for *Mx1*. Effect estimates for additive, maternal, inbred, and epistatic effects, including sex-specific effects, are presented as highest posterior density intervals (in percent starting weight) in 8-12 week old mice ( $n=1,042$ ) after including random effect  $\mu(Mx1 \text{ diplo})$ . Parameters are labeled according to the methods, and intervals are presented as in Figure 4A. Symmetric epistatic, asymmetric epistatic, and sex-specific parameters are indicated by “v:”, “w:”, and “f:”, respectively. The overall treatment effect  $\theta$  is -0.193% (-1.128%, 0.707%). (B) Model inclusion probabilities (MIPs) are given (posterior mean  $\pm$  1 s.d.) for effect parameter classes. (C) Treatment response variance projections (TReVarPs), a generalization of heritability to the diallel effects classes, are shown for three overall effects, five random effects classes, and five corresponding sex-specific random effects classes (with posterior median and 95% HPDs).



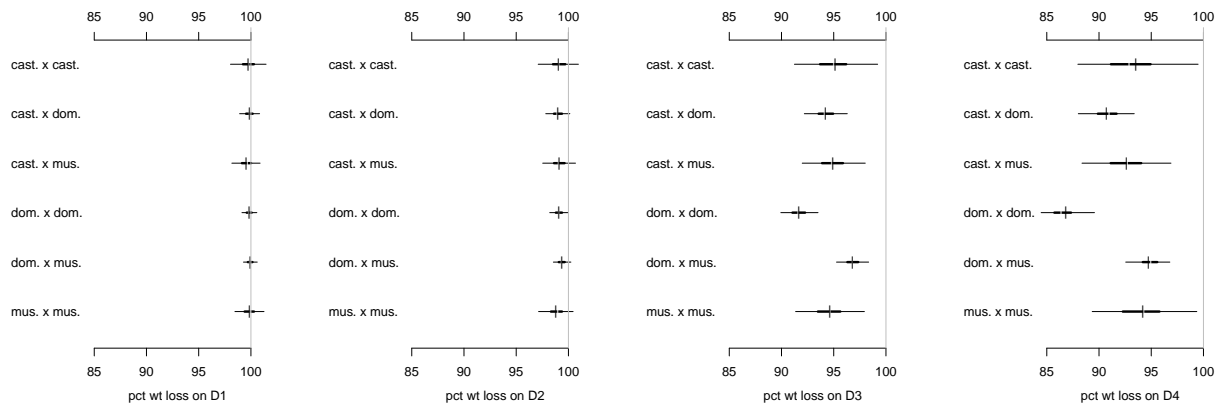
**Figure S12** Diallel effects on host infection response (weight change) at D2 post-infection, using multiple imputation matched quartets and accounting for *Mx1*. Effect estimates for additive, maternal, inbred, and epistatic effects, including sex-specific effects, are presented as highest posterior density intervals (in percent starting weight) in 8-12 week old mice ( $n=1,042$ ) after including random effect  $\mu(Mx1 \text{ diplo})$ . Parameters are labeled according to the methods, and intervals are presented as in Figure 4A. Symmetric epistatic, asymmetric epistatic, and sex-specific parameters are indicated by "v.", "w.", and "f.", respectively. The overall treatment effect  $\theta$  is -0.925% (-1.991%, 0.113%). (B) Model inclusion probabilities (MIPs) are given (posterior mean  $\pm$  1 s.d.) for effect parameter classes. (C) Treatment response variance projections (TRVarPs), a generalization of heritability to the diallel effects classes, are shown for three overall effects, five random effects classes, and five corresponding sex-specific random effects classes (with posterior median and 95% HPDs).



**Figure S13** Diallel effects on host infection response (weight change) at D3 post-infection, using multiple imputation matched quartets and accounting for *Mx1*. Effect estimates for additive, maternal, inbred, and epistatic effects, including sex-specific effects, are presented as highest posterior density intervals (in percent starting weight) in 8-12 week old mice ( $n=514$ ) after including random effect  $u_i^{(Mx1 \text{ diplo})}$ . Parameters are labeled according to the methods, and intervals are presented as in Figure 4A. Symmetric epistatic, asymmetric epistatic, and sex-specific parameters are indicated by “v:”, “w:”, and “f:”, respectively. The overall treatment effect  $\theta$  is -5.429% (-7.675%, -3.102%). (B) Model inclusion probabilities (MIPs) are given (posterior mean  $\pm$  1 s.d.) for effect parameter classes. (C) Treatment response variance projections (TRVarPs), a generalization of heritability to the diallel effects classes, are shown for three overall effects, five random effects classes, and five corresponding sex-specific random effects classes (with posterior median and 95% HPDs).

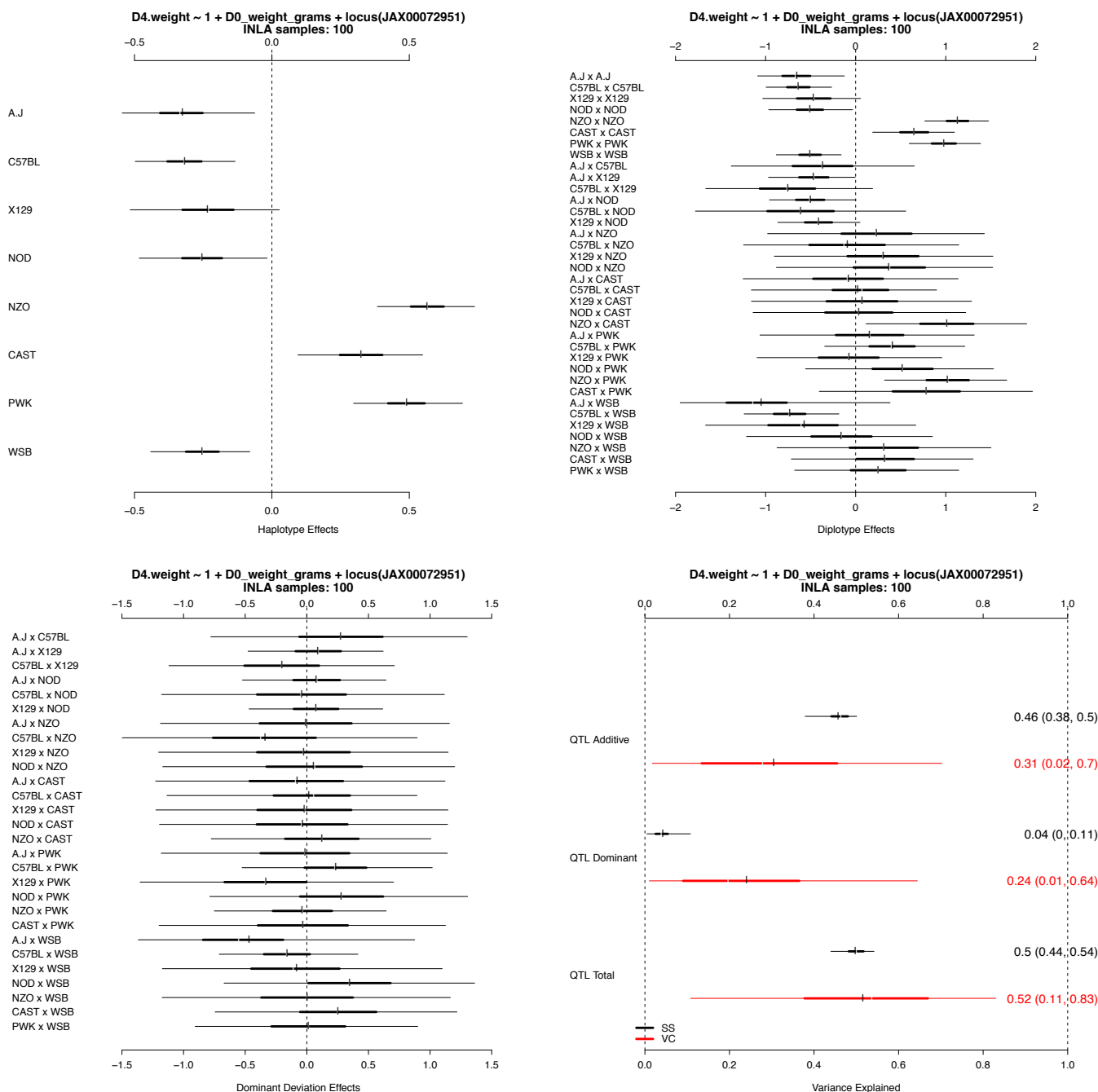


**Figure S14** Diallel effects on host infection response (weight change) at D4 post-infection, using multiple imputation matched quartets and accounting for *Mx1*. Effect estimates for additive, maternal, inbred, and epistatic effects, including sex-specific effects, are presented as highest posterior density intervals (in percent starting weight) in 8-12 week old mice ( $n=513$ ) after including random effect  $u_i^{(Mx1 \text{ diplo})}$ . Parameters are labeled according to the methods, and intervals are presented as in Figure 4A. Symmetric epistatic, asymmetric epistatic, and sex-specific parameters are indicated by “v:”, “w:”, and “f:”, respectively. The overall treatment effect  $\theta$  is -7.986% (-11.202%, -4.147%). (B) Model inclusion probabilities (MIPs) are given (posterior mean  $\pm$  1 s.d.) for effect parameter classes. (C) Treatment response variance projections (TRVarPs), a generalization of heritability to the diallel effects classes, are shown for three overall effects, five random effects classes, and five corresponding sex-specific random effects classes (with posterior median and 95% HPDs).

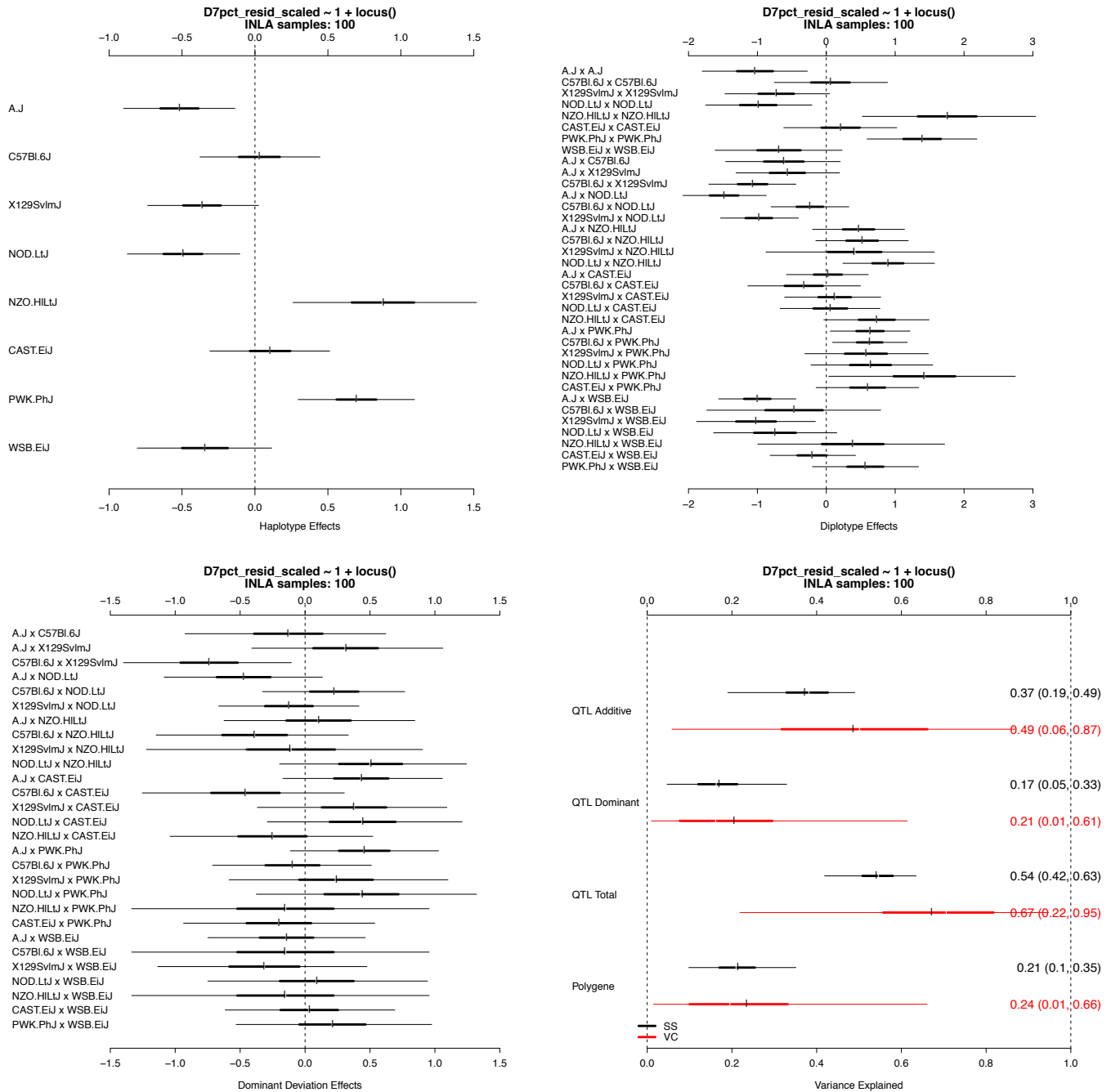


**Figure S15** Timecourse of posterior predictive estimates of for *Mx1* diplotype mean effects across four days post-infection. From left to right, predictive estimates of IAV-induced weight change are provided for D1, D2, D3 and D4 p.i.





**Figure S16** *Mx1* effects and proportion of variance explained on weight loss in the pre-CC. [Top Left] Additive *Mx1* haplotype effects in pre-CC mice (n=155) infected with IAV (PR8) at day 4 post-infection. [Top Right] Bayesian credible intervals of the posterior predictive distribution of mice with *Mx1* diplotype. [Bottom Left] Dominance deviation *Mx1* effects in the pre-CC mice. Wide intervals are indicative of the low levels of heterozygosity observed in the mostly inbred pre-CC mice. [Bottom Right] Bayesian credible intervals of the posterior predictive distribution of the proportion of the phenotypic variance explained by the *Mx1* additive effects, dominant effects and the combination of both effects. Black intervals (VC) are based on the posterior samples of the variance components. Red intervals (SS) are based on the posterior samples of sums of squares estimators. SS estimators are (1) not dependent on variance component estimates, which tend to be disperse, and (2) are based on the observed strains and crosses, rather than all possible strains/crosses, with (1) and (2) resulting in much narrower confidence intervals.



**Figure S17** *Mx1* allele effects and proportion of variance explained on weight loss in the CC-RIX. [Top Left] Additive *Mx1* haplotype effects in CC-RIX mice ( $n=1,402$ ) infected with IAV (CA04) at day 7 post-infection. [Top Right] Bayesian credible intervals of the posterior predictive distribution of mice with *Mx1* diplotype. [Bottom Left] Dominance deviation *Mx1* effects in the CC-RIX mice. Narrower intervals compared to observed in pre-CC is indicative of the high levels of heterozygosity CC-RIX mice. [Bottom Right] Bayesian credible intervals of the posterior predictive distribution of the proportion of the phenotypic variance explained by the *Mx1* additive effects, dominant effects, the combination of both *Mx1* effects, and cumulative effects of other loci captured in the relationship matrix. In the CC-RIX, the relationship matrix models the expected increased phenotypic correlation between CC-RIX mice that share a single CC parent. Black intervals (VC) are based on the posterior samples of the variance components. Red intervals (SS) are based on the posterior samples of sums of squares estimators. SS estimators are (1) not dependent on variance component estimates, which tend to be disperse, and (2) are based on the observed strains and crosses, rather than all possible strains/crosses, with (1) and (2) resulting in much narrower confidence intervals.

■ **Table S1 Proportion of variance in IAV-induced weight loss attributable to diallel effect classes across 4 days post-infection.** Part C of **Figure S7** through **Figure S10** show Bayesian confidence interval plots of treatment response variance projection (TReVarP) values presented here.

Effect Class <sup>a</sup>	D1	0.025	0.975	D2	0.025	0.975	D3	0.025	0.975	D4	0.025	0.975
additive	0.0229	-0.0007	0.0565	0.0197	0.0002	0.0516	0.2163	0.0692	0.3612	0.3477	0.1896	0.4907
maternal	0.0192	0.0011	0.0474	0.0253	0.0030	0.0603	0.0381	0.0021	0.0965	0.0196	0.0000	0.0589
inbred (overall)	0.0306	0.0000	0.0723	0.0142	0.0000	0.0465	0.0025	0.0000	0.0211	0.0021	0.0000	0.0179
inbred	0.0082	-0.0021	0.0299	0.0064	-0.0017	0.0292	0.0031	-0.0136	0.0336	0.0023	-0.0134	0.0304
symmetric epistatic	0.0605	0.0137	0.1190	0.0433	0.0053	0.1008	0.0655	-0.0060	0.2239	0.0692	-0.0095	0.2117
asymmetric epistatic	0.0264	0.0043	0.0598	0.0233	0.0017	0.0608	0.0203	-0.0008	0.0698	0.0163	-0.0009	0.0667
female (overall)	0.0296	-0.0001	0.0669	0.0282	-0.0002	0.0664	0.0299	-0.0010	0.0786	0.0256	-0.0005	0.0692
sex-by-additive	0.0309	0.0038	0.0696	0.0169	0.0008	0.0468	0.0131	-0.0011	0.0506	0.0103	-0.0003	0.0455
sex-by-maternal	0.0143	-0.0002	0.0382	0.0224	0.0004	0.0602	0.0230	-0.0004	0.0751	0.0059	-0.0007	0.0259
female inbred (overall)	0.0024	-0.0025	0.0199	0.0027	-0.0027	0.0210	0.0047	-0.0030	0.0311	0.0027	-0.0028	0.0231
sex-by-inbred	0.0054	-0.0020	0.0278	0.0024	-0.0014	0.0156	0.0034	-0.0015	0.0382	0.0012	-0.0013	0.0194
sex-by-symm. epis.	0.0152	0.0006	0.0454	0.0100	-0.0001	0.0362	0.0089	-0.0008	0.0541	0.0052	-0.0010	0.0366
sex-by-asyymm. epis.	0.0259	0.0018	0.0714	0.0218	-0.0006	0.0747	0.0119	-0.0031	0.0764	0.0059	-0.0009	0.0438
total explained	0.3276	0.2277	0.4260	0.2775	0.1845	0.3813	0.5164	0.3516	0.6866	0.5705	0.4176	0.7206
noise	0.6724	0.5740	0.7723	0.7225	0.6187	0.8155	0.4836	0.3134	0.6484	0.4295	0.2794	0.5824

<sup>a</sup> To indicate the relative contribution of different diallel effects on host response to IAV, TReVarPs are given for overall effects (female, inbred, female inbred) and strain/strainpair-specific effects (additive, maternal, inbred, symmetric epistatic, asymmetric epistatic) on D1delta through D4delta (median and 95% HPD intervals).

**Table S2 Proportion of variance in IAV-induced weight loss attributable to diallel effect classes across 4 days post-infection, after accounting for *Mx1* diplotype.** Part C of **Figure S11** through **Figure S14** show Bayesian confidence interval plots of treatment response variance projection (TReVarP) values presented here.

Effect Class <sup>a</sup>	D1	0.025	0.975	D2	0.025	0.975	D3	0.025	0.975	D4	0.025	0.975
additive	0.0292	-0.0007	0.0809	0.0233	-0.0011	0.0624	0.0631	0.0025	0.1802	0.0496	-0.0008	0.2343
maternal	0.0188	0.0002	0.0455	0.0250	0.0026	0.0601	0.0530	0.0047	0.1273	0.0309	0.0003	0.0916
inbred (overall)	0.0318	0.0000	0.0816	0.0183	0.0000	0.0587	0.0215	0.0000	0.0849	0.0062	0.0000	0.0467
inbred	0.0087	-0.0024	0.0328	0.0064	-0.0021	0.0298	0.0052	-0.0055	0.0381	0.0054	-0.0059	0.0425
symmetric epistatic	0.0639	0.0150	0.1276	0.0450	0.0050	0.1054	0.0286	-0.0025	0.1047	0.0333	-0.0024	0.1353
asymmetric epistatic	0.0260	0.0045	0.0596	0.0227	0.0014	0.0592	0.0272	-0.0014	0.0922	0.0268	-0.0012	0.1067
female (overall)	0.0288	-0.0003	0.0655	0.0280	-0.0001	0.0661	0.0395	-0.0005	0.1001	0.0393	-0.0008	0.1040
sex-by-additive	0.0308	0.0034	0.0696	0.0168	0.0009	0.0467	0.0167	-0.0010	0.0628	0.0152	-0.0010	0.0679
sex-by-maternal	0.0138	0.0000	0.0373	0.0219	0.0002	0.0585	0.0286	-0.0003	0.0931	0.0089	-0.0012	0.0385
female inbred (overall)	0.0023	-0.0026	0.0190	0.0026	-0.0028	0.0210	0.0056	-0.0042	0.0366	0.0040	-0.0043	0.0342
sex-by-inbred	0.0053	-0.0018	0.0269	0.0023	-0.0014	0.0154	0.0041	-0.0021	0.0462	0.0017	-0.0020	0.0241
sex-by-symm. epis.	0.0147	-0.0001	0.0447	0.0100	-0.0006	0.0354	0.0132	-0.0014	0.0811	0.0088	-0.0014	0.0666
sex-by-asymm. epis.	0.0257	0.0017	0.0713	0.0213	-0.0006	0.0734	0.0165	-0.0021	0.1099	0.0091	-0.0017	0.0669
total explained	0.3389	0.2373	0.4435	0.2866	0.1907	0.3939	0.4186	0.2488	0.6053	0.3381	0.1740	0.5365
noise	0.6611	0.5565	0.7627	0.7134	0.6061	0.8093	0.5814	0.3947	0.7512	0.6619	0.4635	0.8260

<sup>a</sup> To indicate the relative contribution of different diallel effects on host response to IAV, TReVarPs are given for overall effects (female, inbred, female inbred) and strain/strainpair-specific effects (additive, maternal, inbred, symmetric epistatic, asymmetric epistatic) on D1delta through D4delta (median and 95% HPD intervals).

■ **Table S3 Model inclusion probabilities for diallel effects classes, (A) before and (B) after accounting for *Mx1* diplotype.** We consider the following levels for strength of evidence for inclusion: positive  $\{(0.05, 0.25] \text{ or } [0.75, 0.95)\}$ , strong  $\{(0.01, 0.05] \text{ or } [0.95, 0.99)\}$  and very strong  $\{[0, 0.01] \text{ or } [0.99, 1]\}$ , as described in the Statistical Methods. Part B of **Figures S7 through S14** show bar plots of posterior MIP values presented here.

(A) Effect Class	D1	D2	D3	D4	(B) Effect Class	D1	D2	D3	D4
theta	1.0000	1.0000	1.0000	1.0000	theta	1.0000	1.0000	1.0000	1.0000
fixed: D0	0.0179	0.4630	0.6074	0.6699	fixed: D0	0.0180	0.4590	0.6319	0.5172
random: batch	0.0772	0.8523	1.0000	0.9999	random: batch	0.0708	0.8332	0.9969	0.9979
					random: <i>Mx1</i> diplo	0.0345	0.5515	1.0000	1.0000
additive	0.0141	0.0494	0.9779	0.9980	additive	0.0120	0.0558	0.3835	0.4305
maternal	0.0082	0.0713	0.7446	0.7400	maternal	0.0068	0.0671	0.6138	0.5272
inbred (overall)	0.3995	0.0164	0.9584	0.9992	inbred (overall)	0.3977	0.0238	0.6696	0.8789
inbred	0.1504	0.2024	0.3050	0.3504	inbred	0.1420	0.2068	0.2737	0.3334
symmetric epistatic	0.2309	0.3305	0.6674	0.9598	symmetric epistatic	0.2195	0.3642	0.5561	0.7668
asymmetric epistatic	0.0366	0.1193	0.8197	0.9662	asymmetric epistatic	0.0318	0.1176	0.6825	0.8511
female (overall)	0.0904	0.1718	0.1719	0.3135	female (overall)	0.0876	0.1762	0.2294	0.3394
sex-by-additive	0.3140	0.1993	0.3174	0.6220	sex-by-additive	0.3051	0.1981	0.2859	0.4884
sex-by-maternal	0.0738	0.3212	0.5550	0.3697	sex-by-maternal	0.0662	0.3194	0.4769	0.2939
female inbred (overall)	0.0237	0.0428	0.1012	0.0943	female inbred (overall)	0.0237	0.0432	0.0913	0.0889
sex-by-inbred	0.2527	0.2325	0.4448	0.3981	sex-by-inbred	0.2466	0.2345	0.3658	0.3345
sex-by-symmetric epistatic	0.1399	0.1694	0.3228	0.5873	sex-by-symmetric epistatic	0.1317	0.1692	0.3028	0.4359
sex-by-asymmetric epistatic	0.2016	0.3683	0.3682	0.4037	sex-by-asymmetric epistatic	0.1924	0.3719	0.3387	0.3296

■ **Table S4** Details of populations analyzed for additive strain-specific effects in **Figure 7**.

POPULATION	diallel	pre-CC	CC-RIX
Recombinant	no	yes	yes
Inbreds	yes (some)	yes	no
Heterozygotes	yes (most)	no	yes
Sexes	males & females	females	females
IAV used	H1N1 (PR8)	H1N1 (PR8)	H1N1 (CA04)
Post-infection day analyzed	day 4	day 4	day 7
Model	Bayes Diallel	Diplofect	Diplofect

■ **Table S5** Table of CC-RIX lines used in this experiment. A total of 1,402 mice from 105 CC-RIX lines (about 13 mice per line), originating from a sparse diallel cross of 65 CC strains, were assayed for weight loss on day 7 post-infection.

CC-RIX ID	count	CC-RIX ID	count	CC-RIX ID	count
CC001xCC055	16	CC020xCC008	17	CC042xCC019	13
CC001xCC074	11	CC021xCC023	15	CC042xCC025	5
CC002xCC011	14	CC021xCC032	3	CC043xCC033	21
CC002xCC021	15	CC022xCC024	11	CC043xCC037	27
CC003xCC051	12	CC022xCC044	3	CC044xCC060	18
CC003xCC062	18	CC023xCC025	18	CC045xCC044	11
CC004xCC011	15	CC024xCC023	15	CC046xCC068	21
CC004xCC012	12	CC024xCC052	11	CC049xCC036	8
CC005xCC001	15	CC025xCC028	20	CC051xCC005	14
CC005xCC040	15	CC026xCC034	17	CC051xCC009	14
CC006xCC007	20	CC026xCC042	7	CC052xCC007	3
CC006xCC039	3	CC027xCC036	3	CC052xCC014	15
CC007xCC070	12	CC027xCC045	14	CC055xCC028	21
CC008xCC009	3	CC028xCC024	21	CC056xCC033	20
CC008xCC010	16	CC028xCC030	18	CC057xCC052	16
CC008xCC018	10	CC029xCC027	16	CC058xCC022	17
CC009xCC040	12	CC029xCC071	6	CC059xCC065	4
CC010xCC015	21	CC030xCC023	23	CC060xCC006	15
CC010xCC060	9	CC030xCC061	17	CC061xCC025	16
CC011xCC032	13	CC032xCC013	18	CC061xCC026	16
CC011xCC042	15	CC032xCC017	15	CC061xCC039	15
CC012xCC032	12	CC033xCC046	18	CC062xCC046	3
CC012xCC038	20	CC033xCC068	21	CC062xCC072	3
CC013xCC041	28	CC034xCC016	10	CC063xCC001	3
CC014xCC059	4	CC035xCC071	14	CC063xCC002	7
CC015xCC018	12	CC036xCC051	16	CC065xCC010	10
CC015xCC059	15	CC037xCC046	12	CC065xCC072	1
CC016xCC038	18	CC037xCC057	19	CC068xCC043	9
CC016xCC061	13	CC038xCC013	14	CC070xCC003	15
CC017xCC004	13	CC039xCC020	14	CC071xCC053	12
CC017xCC041	16	CC040xCC003	16	CC072xCC063	4
CC018xCC009	19	CC040xCC015	13	CC072xCC075	9
CC018xCC065	16	CC041xCC012	12	CC074xCC058	7
CC019xCC002	19	CC041xCC016	18	CC075xCC021	3
CC019xCC004	16	CC042xCC017	14	CC075xCC035	14

■ **Table S6** Summary of overall and additive effects from **Figures 4A, S7A, S8A, S9A, and S10A**. Posterior median and 95% HPD intervals are provided for D1 through D4 p.i.

<b>Diallel Effect</b>	<b>D1</b>	<b>0.025</b>	<b>0.975</b>	<b>D2</b>	<b>0.025</b>	<b>0.975</b>	<b>D3</b>	<b>0.025</b>	<b>0.975</b>	<b>D4</b>	<b>0.025</b>	<b>0.975</b>
treatment (overall) ( $\theta$ )	-0.131	-0.484	0.223	-0.833	-1.328	-0.318	-5.594	-6.470	-4.729	-8.849	-9.920	-7.779
inbred (overall)	1.258	0.407	2.100	1.212	-0.002	2.413	0.416	-1.641	2.477	-0.524	-3.122	2.018
female (overall)	-0.895	-1.447	-0.362	-1.245	-2.037	-0.460	-1.655	-3.066	-0.220	-2.108	-3.868	-0.295
female inbred (overall)	1.221	-0.269	2.680	1.771	-0.375	3.940	-1.286	-5.052	2.438	-1.077	-5.872	3.559
fixed: D0 weight	-0.135	-0.285	0.017	-0.306	-0.522	-0.093	-0.450	-0.928	0.025	-0.473	-1.061	0.123
additive: AJ	-0.089	-0.641	0.445	-0.016	-0.689	0.647	-2.167	-3.721	-0.611	-2.767	-4.661	-0.864
additive: B6	-0.086	-0.642	0.450	-0.153	-0.845	0.524	-0.606	-2.010	0.801	-0.730	-2.638	1.181
additive: 129	0.270	-0.283	0.840	0.316	-0.379	1.031	0.002	-1.442	1.462	-0.997	-2.878	0.917
additive: NOD	0.115	-0.440	0.667	0.062	-0.608	0.771	-0.827	-2.249	0.601	-1.764	-3.703	0.116
additive: NZO	0.191	-0.363	0.747	0.276	-0.437	1.021	2.536	0.719	4.269	4.066	1.948	6.121
additive: CAST	-0.184	-0.752	0.362	-0.120	-0.812	0.579	0.731	-0.674	2.157	1.235	-0.649	3.092
additive: PWK	-0.149	-0.699	0.411	-0.258	-0.967	0.425	1.698	0.116	3.228	4.061	1.971	6.076
additive: WSB	-0.067	-0.610	0.471	-0.108	-0.809	0.567	-1.350	-2.889	0.157	-3.088	-5.008	-1.176
$\sigma^2$	3.808	2.923	4.786	8.188	6.284	10.182	12.199	6.881	17.899	19.679	12.024	28.777



■ **Table S7** Summary of overall, additive, and *Mx1* effects from **Figures S11A, S12A, S13A, and S14A**. Posterior median and 95% HPD intervals are provided for D1 through D4 p.i.

Diallel Effect	D1	0.025	0.975	D2	0.025	0.975	D3	0.025	0.975	D4	0.025	0.975
treatment (overall) ( $\theta$ )	-0.193	-1.128	0.707	-0.925	-1.991	0.113	-5.464	-7.675	-3.102	-7.986	-11.202	-4.147
inbred (overall)	1.296	0.313	2.276	1.385	0.017	2.738	1.945	-0.417	4.282	1.046	-1.971	4.101
female (overall)	-0.894	-1.435	-0.356	-1.251	-2.039	-0.468	-1.681	-3.061	-0.333	-2.105	-3.905	-0.339
female inbred (overall)	1.224	-0.231	2.705	1.765	-0.364	3.931	-1.221	-4.945	2.312	-1.018	-5.663	3.654
fixed: D0 weight	-0.137	-0.289	0.012	-0.313	-0.528	-0.099	-0.548	-0.996	-0.096	-0.576	-1.155	-0.016
additive: AJ	-0.094	-0.679	0.489	-0.015	-0.718	0.691	-1.147	-2.589	0.112	-0.854	-2.819	0.549
additive: B6	-0.086	-0.664	0.501	-0.145	-0.867	0.567	0.190	-0.980	1.352	0.401	-1.017	1.891
additive: 129	0.272	-0.327	0.873	0.323	-0.404	1.076	0.457	-0.695	1.663	0.174	-1.299	1.600
additive: NOD	0.113	-0.453	0.722	0.067	-0.639	0.799	-0.046	-1.221	1.130	-0.148	-1.769	1.266
additive: NZO	0.167	-0.510	0.859	0.232	-0.576	1.068	0.635	-0.737	2.279	0.447	-1.221	2.979
additive: CAST	-0.137	-0.935	0.619	-0.048	-0.942	0.831	0.267	-1.225	1.866	0.230	-1.545	2.277
additive: PWK	-0.162	-0.857	0.506	-0.303	-1.146	0.493	0.105	-1.273	1.578	0.523	-1.124	3.116
additive: WSB	-0.072	-0.653	0.501	-0.111	-0.836	0.605	-0.514	-1.811	0.650	-0.909	-2.962	0.533
<i>Mx1</i> : cast × cast	-0.043	-1.555	1.470	-0.016	-1.712	1.652	0.511	-2.990	4.202	1.257	-3.773	6.904
<i>Mx1</i> : cast × dom	0.057	-1.077	1.193	-0.089	-1.397	1.183	-0.311	-3.008	2.256	-1.287	-5.596	2.401
<i>Mx1</i> : cast × mus	-0.238	-1.572	1.028	0.036	-1.409	1.521	0.317	-2.619	3.433	0.451	-3.933	5.062
<i>Mx1</i> : dom × dom	0.028	-1.076	1.217	0.015	-1.253	1.290	-2.831	-5.872	-0.131	-5.274	-9.857	-0.779
<i>Mx1</i> : dom × mus	0.135	-0.897	1.213	0.290	-0.870	1.522	2.198	-0.207	4.743	2.624	-1.118	6.299
<i>Mx1</i> : mus × mus	0.061	-1.251	1.445	-0.234	-1.817	1.213	0.016	-3.171	3.295	1.948	-2.574	7.167
$\sigma^2$	3.797	2.913	4.769	8.190	6.328	10.268	11.270	6.644	16.627	19.296	12.210	27.397

■ **Table S8** Summary of dominance index for *Mx1* from *cast* or *mus*, combined with *Mx1* from *dom* in our diallel study. Posterior mode and 80% HPD intervals are provided from D1 through D4 p.i. The posterior mode is obtained from the value of  $\mathcal{D}$  that has the maximum posterior density within the range  $[-1, 2]$ , via the `density` function from the `stats` package in R.

index	D1	D2	D3	D4
$\mathcal{D}^{(cast; dom)}$	0.726 (-1.322, 2.676)	0.708 (-1.476, 2.833)	0.421 (-0.534, 0.907)	0.491 (-0.028, 0.836)
$\mathcal{D}^{(mus; dom)}$	0.650 (-1.181, 2.460)	0.832 (-1.410, 3.101)	-0.278 (-2.547, 0.329)	0.068 (-0.568, 0.381)
$\mathcal{D}^{(cast; mus)}$	0.468 (-2.060, 3.042)	0.521 (-2.037, 2.966)	0.450 (-1.884, 2.794)	0.526 (-2.197, 3.135)

**Algorithm 1: Multiple Imputation Matched Quartets (MIMQ)****Data:** Treatment diallel data frame ( $T$ )**Result:** Posterior effect estimates for phenotypes in  $P$ 

```

1  $P \leftarrow$  phenotypes (e.g.  $\text{pct}^{\text{D1}}, \dots, \text{pct}^{\text{D4}}$ );
2  $D \leftarrow$  diallel categories ( $\{j, k, s, h\}$ );
3  $R \leftarrow$  total number of replicates ( $n = 1000$ );
4  $C \leftarrow$  covariates;
5 for  $p \in P$  do
6   for  $d \in D$  do
7     Identify number of individuals to be deleted from this
      class (0-1); if  $> 0$ , add class to set of classes to have
      deletions ( $D_{\text{delete}}$ )
8     Identify number of individuals to be imputed from
      this class (0-3); if  $> 0$  add class to set of classes to
      have imputation ( $D_{\text{impute}}$ )
9   end
10  for  $r \leftarrow 1$  to  $R$  do
11    Make copy of  $T$ :  $T^{(r)}$ 
12    for  $d \in D_{\text{delete}}$  do
13      Randomly delete row from class  $d$  in  $T^{(r)}$ ;
14    end
15    for  $c \in C$  do
16      Obtain diallel effect ( $\hat{\beta}_c$ ) and variance ( $\hat{\sigma}_c^2$ )
      estimates by fitting covariate data for  $c$  with
      BayesDiallel;
17      for  $d \in D_{\text{impute}}$  do
18        Insert row(s) for class  $d$  into  $T^{(r)}$ , imputing  $c_d$ 
        according to the following:  $\tilde{c}_d^r \sim N(\mathbf{d}\hat{\beta}_c, \hat{\sigma}_c^2)$ ;
        based on counts from (8), multiple rows with
        different  $c_d$  values may be inserted;
19      end
20    end
21    Obtain diallel effect ( $\hat{\beta}_p$ ) and variance ( $\hat{\sigma}_p^2$ ) estimates
    by fitting phenotype data for  $p$  with BayesDiallel,
    conditional on imputed covariate(s);
22    for  $d \in D_{\text{impute}}$  do
23      Impute  $p_d$  into phenotype column of respective
       $T^{(r)}$  row(s) according to the following:
       $\tilde{p}_d^r | \tilde{c}_d^r \sim N(\mathbf{d}\hat{\beta}_p, \hat{\sigma}_p^2 | \tilde{c}_d^r)$ 
24    end
25    Run BayesDiallel on  $T^{(r)}$ ;
26  end
27  Concatenate MCMC results from each of the  $T^{(r)}$  runs
  and summarize;
28 end

```