Genet. Res., Camb. (2014), vol. 96, e008. © Cambridge University Press 2014
doi:10.1017/S001667231400010X

Bayesian analysis of additive epistasis arising from new mutations in mice

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(*Received 17 February 2014; accepted 15 June 2014*)

Summary

The continuous uploading of polygenic additive mutational variability has been reported in several studies in laboratory species with an inbred genetic background. These studies have focused on the direct contribution of new mutations without considering the possibility of epistatic effects derived from the interaction of new mutations with pre-existing polymorphisms. In this work we focused on this main topic and analysed the statistical and biological relevance of the epistatic variance for 9 week body weight in two populations of inbred mice. We developed a new linear mixed model parameterization where founder-related additive genetic variability, additive mutational variability and the interaction terms between both sources of variation were accounted for under a Bayesian design and without requiring the inversion of a matrix of epistatic genetic covariances. The analyses focused on a six-generations data set from C57BL/6J mice ($n=3736$) and a five-generations data set from C57BL/6J$^{hg/hg}$ mice ($n=2843$). The deviance information criterion (DIC) clearly favoured the model accounting for epistatic variability with reductions larger than 50 DIC units in both populations. Modal estimates for founder related, mutational and epistatic heritabilities were 0·068, 0·011 and 0·095 in C57BL/6J and 0·060, 0·010 and 0·113 in C57BL/6J$^{hg/hg}$, ruling out any doubt about the biological relevance of epistasis originating from new mutations in mice. These results contribute new insights on the relevance of epistasis in the genetic architecture of mammals and serve as an important component of an additional source of genetic heterogeneity for inbred strains of laboratory mice.

1. Introduction

Although mutation is the ultimate source of polygenic variation, i.e., the raw material for the maintenance of genetic variability (Hill, 1982b), little is known about its role and real contribution to the genetic variability in mammals. Previous analyses characterized this phenomenon in terms of the mutational input of genetic variance per generation (σ^2_m), a well-defined genetic parameter contributing less than 1% of the phenotypic variance (Lynch, 1988; Houle *et al.*, 1996). Although polygenic mutational studies have mainly been conducted on invertebrate laboratory species (Hill, 1982a; Caballero *et al.*, 1991), the relevant contribution of σ^2_m on the phenotypic variance of quantitative traits has also been described in mice (Bailey, 1959; Festing, 1973; Keightley & Hill, 1992; Caballero *et al.*, 1995) and sheep (Casellas *et al.*, 2010). Nevertheless, these σ^2_m estimates cannot be considered as biologically irrelevant, as demonstrated by the successful response to artificial selection reported in some highly inbred lines (Hill, 1982a, 2005; Keightley, 1998). Recent results focused on the accumulation of within-generation mutational variability revealed a remarkable source of additive genetic variability representing up to 4% of the phenotypic variance for litter size in inbred mice (Casellas & Medrano, 2008).

The effect of new mutations cannot be simplified to only accounting for a direct additive contribution of the gene itself, but it must also account for important novel epistatic interactions between genes. Our knowledge on physiological genetics strongly suggests that interaction among gene products is ubiquitous

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(Wright, 1980). New mutations must be part of this epistatic component although research has not been conducted in this field. The contribution of epistasis to genetic variance components remains obscure due to methodological complexities (Crow & Kimura, 1970; Goodnight, 1987, 1988; Wade, 1992; Cheverud & Routman, 1995) and the limited contribution of epistasis to the covariance among relatives (Cockerham, 1954; Hayman & Mather, 1955; Falconer, 1989). Experimental results remain controversial (Simons & Crow, 1977; Barker, 1979), although some studies have reported large contributions to the phenotypic variance (Peripato *et al.*, 2005; Leamy *et al.*, 2008), they account for more than 25% of the variability. In any case, the influence of new mutations was not considered in these studies and thus, the epistatic contribution linked to the continuous uploading of new mutations variance remains unknown.

A basic assumption in studies involving inbred strains of laboratory species is that inbred individuals are genetically homogeneous across generations (Taft *et al.*, 2006; Stevens *et al.*, 2007). In addition to the direct additive variability generated by mutation (Niu & Liang, 2009), the genetic homogeneity can be seriously impaired if new mutational epistasis had a relevant contribution to the phenotypic variability of any quantitative trait of interest. In addition, the study of mutational epistasis contributes information relevant to livestock production systems where both non-additive contributions and mutational additive effects were recently revealed (Casellas *et al.*, 2010; Su *et al.*, 2012).

The study of mutational epistatic effects opens an interesting research field within the context of animal genomics with potential implications for both basic genetics research and applied animal production. The purpose of the present investigation was to analyse epistatic interactions between new mutational additive genetic effects and the genetic background inherited from the founder populations, taking body weight of two mice data sets as example. An appropriate linear mixed model parameterization was developed to properly account for the different genetic sources of variation, and the model was solved by Bayesian inference.

2. Materials and methods

(i) *Mice data sets*

This research focused on the genetic interaction between founder-related additive polygenic effects and new additive genetic variability arising from mutation. Within-generation founder-related additive genetic variance decreases with the number of generations in inbred mice, these variances becoming almost null after a few generations of full-sib mating (Casellas & Medrano, 2008; Casellas *et al.*, 2010). In order to avoid biases due to the absence of founder-related additive genetic variance in more recent generations, our analyses was performed on subsets of mouse data spanning few (five or six) generations, although with a large number of mice per generation. These restrictions provided large founder populations where the additive genetic variance was properly assessed (Table 1). On the other hand, contribution of epistasis is typically assumed small and absorbed into the founder-related additive genetic component (Cheverud & Routman, 1995; Hill *et al.*, 2008; Crow, 2010). Note that founder-specific genetic variance must be clearly smaller in these highly inbred populations than in regular populations, allowing for a more efficient differentiation between both sources of genetic variance. Although confusion between epistasis and other sources of additive genetic variability cannot be completely discarded, final estimates must be seen as minimum boundaries for epistasis in these populations.

As described by Casellas & Medrano (2008), a C57BL/6J (B6) inbred mouse strain was kept in the vivarium of the University of California (Davis, CA) between October 1988 and May 2005. This population was founded by the acquisition of two B6 males and six B6 females from The Jackson Laboratory (Bar Harbor, ME) and evolved during 46 non-overlapping generations. Our analyses focused on a B6 subpopulation derived and expanded from mice born in the 21st generation (Table 1, generation G1) and maintained during five non-overlapping generations (Table 1, generations G2 to G6) without additional contributions from the main B6 line or other outside populations. Whereas the main B6 line was maintained with a reduced number of litters per generation (five to 47 litters), this subpopulation involved 701 litters and 3765 mice in a short period of six generations. Mice were housed in polycarbonate cages under controlled temperature (21 °C ± 2 °C), humidity (40–70%) and lighting (14 hr light, 10 hr dark, lights on at 7 a.m.) conditions and managed according to the guidelines of the American Association for Accreditation of Laboratory Animal Care (http://www.aaalac.org). Only single (one male/one female) and group matings (one male/several females) were used to avoid multiple paternities. Females were housed in individual cages for parturition. Full-sib mating was preferentially used to propagate the population. Pups were individually numbered by ear notching at 2 weeks of age. After weaning (3 weeks) male and female pups were housed in separate cages to avoid uncontrolled matings. Mice were weighted 9 weeks (±2 days) after birth (9WK body weight). All relevant data were recorded accurately in all generations. Sire, dam, dates of mating, birth and weaning, number of pups born and weaned

Table 1. *Summary of pedigree and phenotypic data for the two mice data sets, B6 and B6^{hghg}*

	B6[a] population			($B6^{hg/hg}$)[a] population		
	Mice	Litters	9WK[b] weight, g (mean ± SE)	Mice	Litters	9WK weight, g (mean ± SE)
PEDIGREE DATA						
Generation						
G1	339	62		547	103	
G2	974	160		1025	198	
G3	958	175		675	152	
G4	715	147		447	101	
G5	565	120		216	46	
G6	214	37				
Overall	3765	701		2910	600	
PHENOTYPIC DATA						
Sex						
Male	1497	472	26·92 ± 0·06	1154	348	39·66 ± 0·12
Female	2239	658	21·40 ± 0·04	1689	554	29·29 ± 0·06
Generation						
G1	315	53	23·61 ± 0·19	533	95	33·61 ± 0·27
G2	974	160	23·53 ± 0·11	1001	189	33·14 ± 0·19
G3	955	174	23·65 ± 0·11	660	145	32·78 ± 0·22
G4	715	147	23·19 ± 0·12	433	94	34·26 ± 0·29
G5	563	120	24·20 ± 0·15	216	46	35·60 ± 0·43
G6	214	37	23·71 ± 0·23			
Overall	3736	691	23·61 ± 0·05	2843	569	33·50 ± 0·11

[a] B6 (C57BL/6J), B6$^{hg/hg}$ (C57BL/6J-*hghg*, B6 mice introgressed with the high growth mutation).
[b] 9WK weight: body weight at 9 weeks of age.
SE: Standard error.

were recorded for each litter, and identification number, sex and 9WK body weight were recorded for each mouse. Analyses were performed on 3736 mice with 9WK body weight data coming from 691 litters, whereas the pedigree file included 3765 mice with a complete knowledge of all parental and maternal relationships.

On the other hand, the high growth (*hg*) mutation spontaneously arose in a four-way cross involving AKR/J, C3H, C57BL/6J and DBA/2 inbred founders (Bradford, 1971; Bradford & Famula, 1984), and was introgressed into the B6 background (B6$^{hg/hg}$) in 1981 (Bradford & Famula, 1984). This mutation, a 500 kb deletion on mouse chromosome 10 (Horvat & Medrano, 2001; Wong *et al*., 2002), deregulates the growth hormone/insulin-like growth factor 1 system (Medrano *et al*., 1991) and produces a 30–50% post-weaning overgrowth without increasing adiposity (Bradford & Famula, 1984; Corva & Medrano, 2000). Note that the B6$^{hg/hg}$ strain was isogenic to B6, except for the *hg* mutation and a stretch of AKR/J sequence around this mutation (Horvat & Medrano, 1996). The B6$^{hg/hg}$ strain has been maintained for experimental purposes in our vivarium at the University of California (Davis, CA) during more than 150 generations and 5000 litters. Although the number of litters per generation was generally small, our analyses focused on a five-generations expansion of this B6$^{hg/hg}$ strain generated between years 1996 and 1997, involving between 46 and 198 litters per generation (Table 1). Animal husbandry and data collection followed the same procedures defined for the B6 population. Analyses were performed on a pedigree 2910 mice, 2843 of them having 9WK body weight phenotypic information (Table 1).

(ii) *Statistical models*

After appropriate edition, 9WK body weight in B6 and B6$^{hg/hg}$ data sets was modelled under the following hierarchical structure:

$$y = Xb + Z_1p + Z_2a + Z_2m + Z_2(a \times m) + e$$

where e was the column vector of random errors and y was the column vector of phenotypic data linked to systematic (b), permanent environmental (p) and genetic effect (a, m and $a \times m$) by X, Z_1 and Z_2 incidence matrices, respectively. Note that the genetic sources of variation were defined as the additive genetic effect linked to the base generation (a; founder-related additive genetic effect), the new additive variability originated by mutation (m; see Wray (1990) for a detailed description of this genetic effect), and the

epistatic interaction between both terms ($a \times m$). Systematic effects accounted for sex (male or female) and generation number with six and five levels for B6 and $B6^{hg/hg}$ populations, respectively. The permanent environmental effect was defined as the environmental contribution inherent to each group of mice kept in the same cage after weaning.

Our analyses focused on several aspects of the genetic background for WK9 body weight in mice, requiring an accurate specification of the distribution pattern for a, m and $a \times m$ Assuming an infinitesimal polygenic genetic architecture (Bulmer, 1980), a can be assumed to be drawn from a multivariate normal distribution as follows:

$$a|A, \sigma_a^2 \sim MVN(0, A\sigma_a^2)$$

where A is the numerator relationship matrix as defined by Wright (1922), σ_a^2 is the additive genetic variance component and 0 is a column vector or zeros. Following Wray (1990) theoretical developments for new additive mutational variability, m can be modelled under the following multivariate normal distribution:

$$m|M, \sigma_m^2 \sim MVN(0, M\sigma_m^2)$$

where M is the Casellas & Medrano (2008) numerator relationship matrix adapted from Wray (1990) to accommodate new additive mutations, and σ_m^2 is the mutational variance. The $a \times m$ effect is approximated as the additive epistatic interaction between founder-related and new mutational effects on the basis of Cockerham's (1954) model. This interaction is assumed to be sampled from:

$$(a \times m)|H, \sigma_i^2 \sim MVN(0, H\sigma_i^2)$$

where H is the Hadamard product between matrices A and M, and σ_i^2 is the interaction (or epistasis) variance. Note that this parameterization applied to populations under Hardy–Weinberg equilibrium (Hardy, 1908; Weinberg, 1908), whereas these inbred populations were maintained under assorted mating of full-sibs. Nevertheless, this must be viewed as a reasonable equilibrium between biological plausibility and mathematical parameterization. The main complexity of this parameterization relies on the inversion of covariance matrices (A^{-1}, M^{-1} and H^{-1}), an essential step for the proper construction of the mixed model equations (Henderson, 1973). Matrices A^{-1} and M^{-1} converge to a well-known structure that can be constructed with low computational requirements from a list of parents (Henderson, 1976; Quaas, 1976; Wray, 1990; Casellas & Medrano, 2008), without requiring direct matrix inversion. Conversely, we lacked the simplified rules for constructing H^{-1} and the direct inversion of H becomes mandatory, resulting in high computational time requirements for medium to large populations. Although these computational demands for obtaining H^{-1} would not be a decisive limitation for our analyses, alternative parameterizations avoiding the direct inversion of H could be of special interest for larger data sets.

The previous hierarchical mixed model can be rewritten as follows:

$$y = Xb + Z_1p + Z_2a + Z_2m + Z_2(Hi) + e$$

where $i = H^{-1}(a \times m)$, the new interaction term i comes from a multivariate normal distribution:

$$i|H, \sigma_i^2 \sim MVN(0, H^{-1}HH^{-1}\sigma_i^2) = MVN(0, H^{-1}\sigma_i^2)$$

and only $(H^{-1})^{-1} = H$ is required for the proper construction of the mixed model equations. This alternative parameterization of the mixed model equations was described by Henderson (1984), although under standard genetic evaluation models. Note that H can be constructed from A and M, and both A and M are obtained by the tabular method (Wright, 1922) or other computationally efficient approaches. After obtaining i, the $a \times m$ term can be calculated in a straightforward manner by applying the following relationship:

$$(a \times m) = Hi$$

It is important to note that the variance component (σ_i^2) does not undergo any modification during this reparameterization, leading to a direct calculation of the heritability for additive epistatic effects (h_i^2; i.e., the percentage of total phenotypic variance accounted for by σ_i^2) as follows:

$$h_i^2 = \sigma_i^2 / \left(\sigma_a^2 + \sigma_m^2 + \sigma_i^2 + \sigma_p^2 + \sigma_e^2\right)$$

Both additive (h_a^2) and mutational (h_m^2) heritabilities can be calculated in a similar way by appropriately replacing the numerator σ_i^2 by σ_a^2 and σ_m^2, respectively. Despite current parameterization assuming null genetic correlations between a, m and $a \times m$, we must be cautious because breeding values become linear functions of mutation effects (Wray, 1990); collinearity must be evaluated among the genetic effects included in the model in order to determine their robustness and accuracy. Within this context, Pearson correlation coefficients were computed between each pairwise combination of a, m, $a \times m$ and e, and their posterior distributions were evaluated as indicators of relatedness between genetic effects. High and positive correlations would suggest a high degree of collinearity, whereas null or almost null estimates must indicate independence.

(iii) *Bayesian analyses*

Within a Bayesian development, the joint posterior distribution of our model was proportional to the

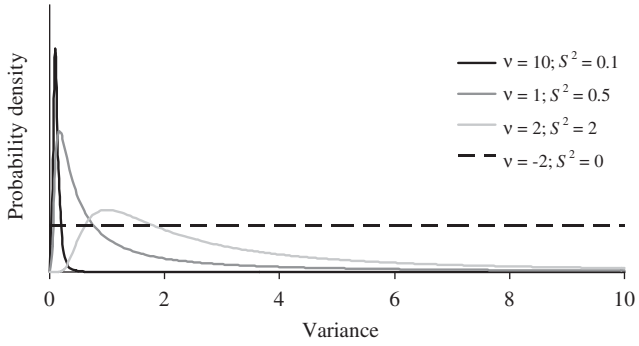

Fig. 1. *A priori* distributions for genetic variance components analyzed using scaled χ^{-2} priors with hyperparameters $v=10$ and $S^2=0{\cdot}1$ (PR1), $v=1$ and $S^2=0{\cdot}5$ (PR2), $v=2$ and $S^2=2$.

likelihood of the data multiplied by the *a priori* probabilities of the unknown parameters of the model:

$$p(b,p,a,m,i,\sigma_e^2,\sigma_e^2,\sigma_e^2,\sigma_e^2,\sigma_e^2|y)\propto$$
$$p(y|b,p,a,m,i,\sigma_e^2)p(b)p\left(p\middle|\sigma_p^2\right)p\left(\sigma_p^2\right)$$
$$\times\, p(a|A,\sigma_a^2)p(\sigma_a^2)p(m|M,\sigma_m^2)p(\sigma_m^2)p(i|H,\sigma_i^2)p(\sigma_i^2)p(\sigma_e^2)$$

The likelihood of WK9 body weight data was defined as multivariate normal:

$$p(y|b,p,a,m,i,\sigma_e^2)$$
$$= MVN\left(Xb+Z_1p+Z_2a+Z_2m+Z_2(Hi),I_e\sigma_e^2\right),$$

With I_e being an identity matrix with dimensions equal to the number of phenotypic data. The *a priori* distribution of P was assumed to be drawn from another multivariate normal density:

$$p\left(p\middle|\sigma_p^2\right)=MVN\left(0,I_p\sigma_p^2\right),$$

Where I_p is an identity matrix with dimensions equal to the number of elements in P, and the genetic effects (a, m and $a\times m$) were modelled under the multivariate normal distributions previously defined in the earlier sections of this manuscript. Flat priors were assumed for b, σ_e^2 and σ_p^2. To evaluate the effect of *a priori* information on σ_a^2, $\sigma_m{}^2$ and σ_i^2, four different scaled inverted χ^2 prior distributions with hyperparameters v and S^2 were assumed (Fig. 1) and tested independently on our data sets (see below). Given the almost null previous knowledge about the expected distribution of σ_a^2, σ_m^2 and σ_i^2, these four independent scaled χ^{-2} priors depicted a wide range of plausible scenarios with a decreasing level of stringency for the distribution of the variance component. Whereas prior 1 ($v=10$; $S^2=0{\cdot}1$) has a narrow probability close to the null estimate, prior 4 ($v=-2$; $S^2=0$) converged to uniform distribution between 0 and $+\infty$, ignoring previous knowledge and providing the same *a priori* probability to all values within the parametric space.

In order to elucidate the biological and statistical relevance of the additive genetic effects, analyses were performed under a three-step approach (see below). During this process, the statistical performance of all models was evaluated and compared in terms of goodness of fit and predictive ability. The first comparison, i.e., goodness of fit, was carried out by the deviance information criterion (DIC), a Bayesian statistic integrating information from both models fit to real data and mathematical complexity in terms of number of parameters (Spiegelhalter *et al*., 2002). Models with smaller DIC were favoured as this indicated a better model fit and a lower degree of model complexity. Differences larger than 3–5 DIC units are typically assumed as relevant (Spiegelhalter *et al*., 2002, 2003). On the other hand, the prediction of future records given past data is a question of concern that can be answered using the concept of predictive density, a notion that arises naturally in Bayesian statistics (Matos *et al*., 1997). To estimate predictive ability, a new data set was generated by removing 50% of the records. Both mean square error (MSE) and correlation coefficient ($\rho_{y,\tilde{y}}$) were computed between expectations from the predictive distribution and the removed records (see Casellas *et al*. (2007) for a detailed description of the calculation of MSE and $\rho_{y,\tilde{y}}$).

During the first step, a reference model without additive genetic effects (Model 0) was analysed. This model assumed the same hierarchical structure and *a priori* distributions defined for the complex model described above, although arbitrarily fixing a, m and $a\times m$ effects to 0. During the second analytical step, Model 0 was complemented with the inclusion of the a and m effects as unknown parameters of the model (Model AM), although the $a\times m$ term was still fixed to 0. Following Casellas & Medrano (2008), the same *a priori* distribution was assumed for σ_a^2 and σ_m^2 and therefore, four different parameterizations were analysed assuming priors 1, 2, 3 and 4 (Fig. 1). Finally, the Model AM with the smallest DIC value evolved to the inclusion of the $a\times m$ as an additional effect to be estimated (Model E). As for the previous step, the four-scaled inverted χ^2-prior distributions for σ_i^2 were evaluated by four independent analyses. At the end, nine different models were analysed and compared by the DIC, MSE and $\rho_{y,\tilde{y}}$ parameters.

For each model and data set, three independent Monte Carlo Markov chains (MCMC) were launched for sampling for the marginal posterior distribution of each unknown parameter in our analyses. All parameters were updated by Gibbs sampling (Gelfand & Smith, 1990) and each MCMC was composed of 1 050 000 iterations. Chain convergence was checked by visual inspection of σ_i^2 plots (or σ_m^2 for Model 0) and by the Raftery & Lewis (1992) method. Although convergence was reached with less than 1000 iterations in all MCMC, the first 50 000

iterations were discarded. Given the autocorrelation inherent to the successive iterations of Gibbs sampling, only one iteration from each 50 iterations was stored for inference purposes. The posterior distribution of each parameter was constructed with 20 000 values from each of the three MCMC evoking the ergodic property of the chains (Gilks *et al.*, 1996).

3. Results

(i) *Phenotypic data*

The phenotypic characterization of the two mouse inbred strains were the starting point for the characterization of the genetic sources of variation. Average 9WK body weight phenotypic values for B6 and $B6^{hg/hg}$ strains are shown on Table 1. $B6^{hg/hg}$ mice were 9·89 g heavier than B6 mice on average ($p<0{\cdot}001$) and, in a similar way, its raw phenotypic variability increased to 34·40 g^2; note that the phenotypic dispersion for the B6 population was 9·34 g^2. Males were heavier than females in both B6 (+5·52 g; $p=0{\cdot}001$) and $B6^{hg/hg}$ (+10·37 g; $p=0{\cdot}001$) strains and within-generation averages were moderately heterogeneous, providing few differences at $p=0{\cdot}05$. Note that both mouse sex and generation were properly accounted for in the mixed linear models used in this study.

(ii) *Model comparison*

Model 0 lacked additive genetic effects and it was assumed as the starting reference stage for our analyses. This model reached an average DIC value of 13 767·7 and 13 810·0 for B6 and $B6^{hg/hg}$ mice, respectively (Tables 2*a* and 2*b*); moreover, this model also provided maximum estimates for MSE and minimum estimates for $\rho_{y,\tilde{y}}$ when compared with remaining models. Note that these values did not provide information by themselves, but alternative models provide the base to compare remaining estimates. The inclusion of the *a* and *m* effects generalized Model 0 to a model accounting for direct additive genetic effects (model AM). Given the decreasing degree of stringency evoked by the *a priori* distributions assumed for σ^2_a and σ^2_m variances (Fig. 1), the effect of four alternative stages of *a priori* knowledge on the expected values of both variance components were evaluated. Assuming that 3 to 5 DIC units are the minimal departure to report significant differences between two competing models (Spiegelhalter *et al.*, 2002, 2003), Model AM4 was clearly preferred when compared with the null hypothesis characterized by Model 0, as demonstrated by the 395·2 and 291·3 DIC units reduction in B6 and $B6^{hg/hg}$ populations, respectively. The other three parameterizations of Model AM (priors 1, 2 and 3) were slightly penalized (Tables 2*a* and 3*a*) in relation to Model AM4, although DIC, MSE and $\rho_{y,\tilde{y}}$ differences were not relevant within each population. Given these small statistical differences, Model AM was expanded to Model E on the basis of Model AM4.

Model performance under the four alternative *a priori* distributions for σ^2_i provided very similar results on B6 and $B6^{hg/hg}$ data sets. DIC favored Model E4 (13 199·7 and 13 465·1, respectively) with slight and non-relevant advantages on Model E3 (13 202·2 and 13 467·3, respectively). The remaining parameterizations for σ^2_i revealed larger than 5 DIC unit penalizations, discarding the restrictive scenarios drawn by these priors. Both MSE and $\rho_{y,\tilde{y}}$ showed a similar trend, corroborating the advantage of Model E3 and Model E4 in terms of predictive ability too. In conclusion, Model EPI_{PR4} reduced DIC units from Model AM4 by 172·8 (B6 population) and 53·6 ($B6^{hg/hg}$ population), providing decisive evidence about epistasis in our populations.

(iii) *Variance components*

Variance components estimated under Model E3 and Model E4 showed minimal differences and highest posterior density regions at 95% (HPD95) were fully overlapped (results not shown). Variance components were reported on the basis of Model E4 (and Model AM4). Founder-related additive genetic variance was moderate in B6 and $B6^{hg/hg}$ populations, accounting for the 6·8 and 6·0% of the phenotypic variance, respectively. Although modal estimates suggested a slight reduction from the values obtained under Model AM4 (9·2 and 8·2%, respectively), HPD95 were overlapped and discarded any significant departure. On the other hand, σ^2_m was small and represented ~1% of the phenotypic variance in both populations. The final target of our analyses, σ^2_i, was remarkably high in the B6 (0·505) and $B6^{hg/hg}$ (1·192) data sets, with the HPD95 values far from the null estimate. The modal contribution of this variance component to the phenotypic variance was 9·5 and 11·3%, respectively; HPD95 started at values larger than 3% of the phenotypic variance, providing decisive evidence about the biological relevance of epistatic interactions on 9WK body weight in mice. Although a detailed pairwise comparison between the estimates from Model AM4 and Model E4 did not reveal relevant departures in addition to σ^2_i, a small reduction of the σ^2_e, could be suggested in terms of modal estimates. This value suggests that epistatic variability was mainly accumulated in the residual term of Model AM4, without discarding the partial absorption of epistatic effects in the remaining genetic and environmental variance components.

Modal estimates for correlation coefficients between each pairwise comparison of genetic effects

Table 2. *χ^{-2} hyperparameter specifications and model comparison statistics for the C57BL/6J strain under Models 0 and AM (a) and Models E (b). Goodness of fit was assessed by the deviance information criterion (DIC), whereas predictive ability was evaluated by the mean square error and the correlation coefficient between real and predicted data ($\rho_{y,\hat{y}}$)*

		Model AM[a] (depending on priors for σ_a^2 and σ_m^2)			
	Model 0	1	2	3	4
(a)					
χ^{-2} hyperparameters					
v		10	1	2	−2
S^2		0·1	0·5	2	0
DIC					
Chain 1	13 768·4	13 375·1	13 374·7	13 372·2	13 373·6
Chain 2	13 766·9	13 373·5	13 372·8	13 373·9	13 372·5
Chain 3	13 767·7	13 374·0	13 372·5	13 372·9	13 371·4
Mean	13 767·7	13 374·2	13 373·8	13 373·0	13 372·5
SD	0·8	0·8	1·3	0·9	1·1
Mean square error, g					
Chain 1	5·45	5·24	5·20	5·21	5·18
Chain 2	5·51	5·20	5·23	5·19	5·21
Chain 3	5·46	5·25	5·23	5·23	5·17
Mean	5·47	5·24	5·22	5·21	5·19
SD	0·03	0·03	0·02	0·02	0·02
$\rho_{y,\hat{y}}$					
Chain 1	0·563	0·602	0·609	0·615	0·618
Chain 2	0·559	0·608	0·604	0·608	0·615
Chain 3	0·565	0·601	0·605	0·617	0·618
Mean	0·562	0·604	0·606	0·613	0·617
SD	0·003	0·004	0·003	0·005	0·002

	Model E[b] (depending on priors for σ_i^2)			
	1	2	3	4
(b)				
χ^{-2} hyperparameters				
v	10	1	2	−2
S^2	0·1	0·5	2	0
DIC				
Chain 1	13 210·5	13 206·7	13 202·3	13 199·4
Chain 2	13 209·7	13 207·4	13 201·6	13 199·1
Chain 3	13 209·8	13 206·1	13 202·7	13 200·5
Mean	13 210·0	13 206·7	13 202·2	13 199·7
SD	0·4	0·7	0·6	0·7
Mean square error, g				
Chain 1	5·00	4·96	4·87	4·61
Chain 2	5·06	4·95	4·89	4·67
Chain 3	5·07	4·90	4·83	4·66
Mean	5·04	4·94	4·86	4·65
SD	0·04	0·03	0·03	0·03
$\rho_{y,\hat{y}}$				
Chain 1	0·659	0·680	0·692	0·724
Chain 2	0·637	0·681	0·689	0·730
Chain 3	0·636	0·689	0·707	0·728
Mean	0·644	0·683	0·696	0·727
SD	0·013	0·005	0·010	0·003

[a] Mixed linear model including founder-related and mutational genetic effects.
[b] Mixed linear model including founder-related, mutational and epistatic genetic effects.
SD: Standard deviation.

Table 3. *χ^{-2} hyperparameter specifications and model comparison statistics for the C57BL/6J$^{hg/hg}$ strain under Models 0 and AM (a) and Models E (b). Goodness of fit was assessed by the deviance information criterion (DIC), whereas predictive ability was evaluated by the mean square error and the correlation coefficient between real and predicted data ($\rho_{y,\hat{y}}$)*

		Model AM[a] (depending on priors for σ^2_a and σ^2_m)			
	Model 0	1	2	3	4
(a)					
χ^{-2} hyperparameters					
v		10	1	2	−2
S^2		0·1	0·5	2	0
DIC					
Chain 1	13 809·5	13 519·2	13 521·9	13 519·5	13 518·0
Chain 2	13 811·0	13 519·9	13 519·9	13 519·1	13 519·1
Chain 3	13 809·7	13 518·5	13 510·7	13 518·3	13 519·0
Mean	13 810·0	13 519·2	13 520·5	13 519·0	13 518·7
SD	0·8	0·7	1·2	0·6	0·6
Mean square error, g					
Chain 1	11·00	10·07	10·19	9·96	10·02
Chain 2	10·94	10·07	10·12	9·96	9·94
Chain 3	10·92	10·06	10·18	10·04	9·95
Mean	10·95	10·07	10·16	9·99	9·97
SD	0·04	0·01	0·04	0·05	0·04
$\rho_{y,\hat{y}}$					
Chain 1	0·550	0·592	0·580	0·597	0·598
Chain 2	0·551	0·593	0·588	0·596	0·606
Chain 3	0·551	0·592	0·581	0·594	0·605
Mean	0·551	0·592	0·583	0·596	0·603
SD	0·001	0·001	0·004	0·002	0·004

	Model E[b] (depending on priors for σ^2_i)			
	1	2	3	4
(b)				
χ^{-2} hyperparameters				
v	10	1	2	−2
S^2	0·1	0·5	2	0
DIC				
Chain 1	13 476·1	13 471·2	13 467·6	13 465·0
Chain 2	13 475·3	13 469·7	13 467·7	13 465·7
Chain 3	13 475·8	13 470·3	13 466·7	13 464·8
Mean	13 475·7	13 470·4	13 467·3	13 465·1
SD	0·4	0·8	0·6	0·5
Mean square error, g				
Chain 1	9·52	9·35	9·17	8·97
Chain 2	9·51	9·39	9·19	9·02
Chain 3	9·52	9·34	9·15	8·99
Mean	9·52	9·36	9·17	8·99
SD	0·01	0·03	0·02	0·03
$\rho_{y,\hat{y}}$				
Chain 1	0·625	0·652	0·685	0·707
Chain 2	0·627	0·648	0·689	0·699
Chain 3	0·624	0·651	0·684	0·705
Mean	0·625	0·650	0·686	0·704
SD	0·002	0·002	0·003	0·004

[a] Mixed linear model including founder-related and mutational genetic effects.
[b] Mixed linear model including founder-related, mutational and epistatic genetic effects.

(a, m and $a \times m$) were low and positive, ranging from 0·182 (a vs. m; B6) to 0·342 (a vs. $a \times m$; B6). Moreover, correlation coefficients between genetic effects and residual terms (e) were even smaller, the maximum modal estimate being 0·150 (m vs. e; $B6^{hg/hg}$) and the minimum being slightly lower than zero (−0·022; $a \times m$ vs. e; B6). It is important to highlight that HPD95 were wide in all cases and included the null estimate by far; width of HPD95 took values between 0·331 and 0·543 correlation units.

4. Discussion

(i) *Mouse strains and 9WK body weight*

Although a description of raw phenotypes was not the principal aim of this research, phenotypic and pedigree data are the starting point for subsequent genetic analyses; their formal characterization provides essential information for an accurate interpretation of genetic estimates from complex mixed linear analyses. In a similar way, relevant information is contributed by the origin and genetic background inherent to each mouse strain involved in the experimental design. Both B6 and $B6^{hg/hg}$ mice were closely related, since $B6^{hg/hg}$ strain was originated by introgressing the *hg* mutation into the B6 background (Bradford & Famula, 1984). This mutation and a stretch of AKR/J sequence around the mutation (Horvat & Medrano, 1996) were the known genetic differences between these two inbred strains. Nevertheless, B6 and $B6^{hg/hg}$ strains were independently bred for more than 20 generations and new mutations arose separately and accumulated in each strain. On the basis of the results of Casellas & Medrano (2008) and Niu & Liang (2009), departures between B6 and $B6^{hg/hg}$ strains could be by far greater than the anticipated *hg* mutation and AKR/J sequences.

All mice were kept in the same vivarium and under very similar husbandry practices; therefore, phenotypic differences must be mainly due to the loci determining 9WK body weight. $B6^{hg/hg}$ mice were almost 10 g heavier at 9WK than their B6 mice, as expected due to the *hg* mutation (Bradford & Famula, 1984). In a similar way, phenotypic variance was also larger for $B6^{hg/hg}$ mice (34·40 g^2 vs. 9·34 g^2), although this departure in dispersion parameters could not be anticipated by the allelic effect substitution of the *hg* mutation. Note that the inheritance pattern of this mutation was described as recessive with nearly complete penetrance (Bradford & Famula, 1984). Assuming a slight distortion on the $B6^{hg/hg}$ phenotypic variance due to a residual departure from complete penetrance, the increasing phenotypic variability must be related to developmental instability (Vishalakshi & Singh, 2008; Debat *et al*., 2009) and a scale effect, although the accumulation of new genetic variability by mutation cannot be completely discarded (Casellas & Medrano, 2008). Indeed, epistatic QTL for growth and obesity were described between the *hg* mutation and several genomic locations in other chromosomes (Corva *et al*., 2001). This analytical evidence suggested an increasing number of genomic targets sensitive to new mutations in the $B6^{hg/hg}$ background; some new mutations modulating these genomic targets or other steps of the growth hormone/insulin-like growth factor 1 pathway could be responsible for part of this increased phenotypic variability. Given that our research focused on the partition of the phenotypic variance from different genetic and environmental sources, changes in phenotypic variance between our two related strains was of special interest.

(ii) *Mixed linear models and a priori distributions*

Making comparisons between models is a topic of major interest in statistical genetics given the substantial impact that a model can have on statistical inference. This phenomenon is of particular relevance in Bayesian analyses where both model structure and *a priori* information for model parameters could have a deep impact on final conclusions. Whereas experimental data themselves must not be influenced by arbitrary choices, prior distributions are arbitrarily chosen from previous knowledge of the parameters of interest. Given that studies on the epistatic ability of new mutations were not previously conducted, our *a priori* assumptions became a blind choice with unpredictable consequences on the posterior inference (Gianola & Fernando, 1986; Blasco, 2001). Within this frame, our analyses examined model performance in two areas: (1) analysing the relevance of the epistatic interaction term between new mutations and founder-related effects and (2) studying the consistency of different *a priori* assumptions for the genetic variance components.

Assuming a mixed linear model without additive genetic effects as starting point, both B6 and $B6^{hg/hg}$ data sets showed a substantial reduction (increase) of the DIC and MSE ($\rho_{y,\tilde{y}}$) statistics when a and m effects were included. Note that both populations were considered as fully inbred populations, although the presence of two different sources of additive genetic variance impaired the assumption of genetic homogeneity typically made on these inbred strains of mice (Festing, 1979). These results agreed with the previous conclusions of Casellas & Medrano (2008), where a statistically significant and biologically relevant source of genetic variance was detected for litter size in an inbred population of B6 mice. The preliminary comparison of different *a priori* χ^{-2} distributions for σ_a^2 and σ_m^2 did not reveal relevant departures in terms of DIC, MSE and $\rho_{y,\tilde{y}}$. Although DIC

Table 4. *Modal estimates and highest posterior density region at 95% (HPD95) for the variance components and heritabilities for the C57BL/6J (a) and C57BL/6J$^{hg/hg}$ (b) data set*

	Model AM4[b]		Model E4[c]	
Parameter[a]	Mode	HPD95	Mode	HPD95
(a)				
σ^2_q (g^2)	0·384	0·171 to 0·831	0·364	0·190 to 0·800
σ^2_m (g^2)	0·045	0·006 to 0·148	0·058	0·009 to 0·161
σ^2_i (g^2)			0·505	0·248 to 0·998
σ^2_p (g^2)	1·580	1·364 to 1·822	1·529	1·299 to 1·786
σ^2_e (g^2)	2·180	1·766 to 2·649	1·759	1·332 to 2·149
h^2_q	0·092	0·036 to 0·142	0·068	0·010 to 0·155
h^2_m	0·010	0·001 to 0·032	0·011	0·001 to 0·033
h^2_i			0·095	0·033 to 0·187
	Model A4		Model E4	
Parameter	Mode	HPD95	Mode	HPD95
(b)				
σ^2_q (g^2)	0·807	0·457 to 1·319	0·636	0·325 to 1·067
σ^2_m (g^2)	0·091	0·048 to 0·161	0·110	0·047 to 0·192
σ^2_i (g^2)			1·192	0·457 to 2·169
σ^2_p (g^2)	2·318	1·832 to 2·860	2·277	1·774 to 2·813
σ^2_e (g^2)	7·350	6·067 to 8·236	6·343	5·149 to 7·379
h^2_q	0·083	0·032 to 0·116	0·060	0·027 to 0·099
h^2_m	0·009	0·003 to 0·044	0·010	0·003 to 0·042
h^2_i			0·113	0·045 to 0·187

[a] σ^2_q: founder-related additive genetic variance; σ^2_m: mutational variance; σ^2_i: epistatic variance; σ^2_p: permanent environmental variance; σ^2_e: residual variance; h^2_q: founder-related additive heritability; h^2_m: mutational heritability; h^2_i: epistatic heritability.
[b] Mixed linear model including founder-related and mutational genetic effects. Genetic variances were modeled under flat *a priori* distributions within a Bayesian context.
[c] Mixed linear model including founder-related, mutational and epistatic genetic effects. Genetic variances were modeled under flat *a priori* distributions within a Bayesian context.

discrepancies did not reach the 3–5 DIC units suggested by Spiegelhalter *et al.* (2002, 2003), flat *a priori* distributions for σ^2_a and σ^2_m were assumed for further analyses.

The inclusion of the $a \times m$ was also favoured in both data sets (Tables 2 and 3). In this case, the different *a priori* distributions provided some relevant differences in both data sets, reducing the DIC and MSE estimates and increasing the $\rho_{y,\tilde{y}}$ estimate with smoothed χ^{-2} distribution. As for σ^2_a and σ^2_m, Model E4 reached the best performance, although differences with Model E3 were not statistically significant in both data sets. In any case, the small departures observed between the different *a priori* distributions for σ^2_i suggested that the experimental data had enough information content to override moderate influences of prior information, even under very extreme assumptions. As previously reported by Casellas & Medrano (2008), these models including mutational terms seemed to perform better under a vague assumption for genetic variance components over the parameter space.

(iii) *Genetic variability in inbred mouse strains*

Genetic variances were discussed on the basis of Model E4 (and Model AM4) because it reached the smallest DIC and MSE estimates and the largest $\rho_{y,\tilde{y}}$ estimate, and the differences between estimated variance components across *a priori* distributions for genetic variances were minimal (results not shown). In B6 and B6$^{hg/hg}$ mice 9WK body weight was moderately heritable, with σ^2_a accounting for 6·8 and 6·0% of the phenotypic variance, respectively. Our estimates were far from the heritability values obtained in other outbred populations such as beef cattle, i.e., 0·25 (Frizzas *et al.*, 2009), dairy cattle, i.e., 0·48–0·57 (Toshniwal *et al.*, 2008), goats, i.e., 0·35–0·47 (Snyman & Olivier 1999), and mice, i.e., 0·56 (Leamy *et al.*, 2005), although they revealed a high degree of genetic variability for an inbred population. These estimates were accompanied by relevant mutational variances accounting for ~1% of the phenotypic variance (Table 4). Note that estimated mutational heritabilities were close to the upper limit of the values

reviewed by Lynch (1988) and Houle *et al.* (1996), and agreed with mutational heritabilities reported by Caballero *et al.* (1995) in other B6-related mouse strains. As was previously suggested by Casellas & Medrano (2008) in the same B6 population, σ^2_m must be viewed in highly inbred strains as a lower limit for the infinitesimal polygenic genetic variance, although higher σ^2_a estimates can be anticipated depending on the stationary equilibrium reached by mutation and genetic drift phenomena. Given the full-sib mating system applied in our populations, a quick depletion of additive genetic variance could be anticipated and thus, σ^2_a must originate from short-term mutations arising in the few previous generations, these being characterized by σ^2_m (Casellas & Medrano, 2008). Additional genetic mechanisms contributing a low level of genetic variance cannot be discarded, e.g., loci under balancing selection (Crow, 2010), although the relevance of σ^2_m in our experimental populations is of no doubt (Table 4). In any case, this remarkable amount of founder-related and mutational additive genetic variability provided an excellent frame for the study of genetic epistasis between both additive genetic variance components. It is important to highlight that residuals and *a*, *m* and $a \times m$ effects were moderately correlated, although the posterior distribution of these correlation coefficients included the null estimate within the HPD95 in all cases. Nevertheless, a certain degree of collinearity between these genetic and residual sources of variation cannot be completely discarded under the current analytical model, this partially impairing the accuracy of final estimates. This could be anticipated by the original developments of Wray (1990) and relies on the fact that breeding values are linear functions of mutation effects (Wray, 1990) and part of the epistatic effect could be absorbed by founder-related additive genetic effects (Cheverud & Routman, 1995; Hill *et al.*, 2008; Crow, 2010).

Epistasis, the effect due to the interaction between different genes, has been reported in F_2 crosses from inbred mouse strains (Caron *et al.*, 2005; Yi *et al.*, 2006; Leamy *et al.*, 2008) as well as livestock (Barendse *et al.*, 2007; Noguera *et al.*, 2009; Uemoto *et al.*, 2009) and crop species (Silva & Hallauer, 1975; Goldringer *et al.*, 1997; Xu & Jia, 2007). In these studies, epistasis was modelled on a QTL basis (Leamy *et al.*, 2008; Noguera *et al.*, 2009) or as an additional variance component (Caron *et al.*, 2005; Yi *et al.*, 2006). All designs assumed that the epistatic load inherent to each experimental population did not vary during data collection, even when this process spanned several generations. This broad assumption was far from being realistic although it provided the first confirmations on the relevance of epistasis in the genome of several species. Our research was an endeavour to generalize the study of epistasis when new mutations were also accounted for in the analysis and it represents the first experimental evidence for this kind of mutational contribution in the scientific literature (Table 4).

Despite its basic role in evolution and speciation (Cheverud & Routman, 1995), the link between epistasis and mutation is controversial. Our results showed that this link exists without doubt in laboratory mice and accounts for a remarkable percentage of the total phenotypic variance (~10%; Table 4), even larger than the direct contribution of new mutations. Although not more than a hypothesis, this advantage for σ^2_i when comparing with σ^2_m could be related to the possibility of multiple epistatic interactions originating from a unique mutation (i.e., larger variability for σ^2_i), whereas the mutation itself does not contribute more than its direct effect on σ^2_m. Taking Wray (1990) as a starting point, new mutations not only contributed direct effects on 9WK body weight in mice but also interacted with pre-existing polymorphisms in the mouse genome. Note that our analyses focused on a short period of time (i.e., five or six generations) where, even under full-sib mating, σ^2_a was not depleted and allowed for a proper estimation of the interaction term. Nevertheless, these results from inbred mice strains cannot be directly generalized to livestock species where much of the recent additive genetic variance is the result of past and recent selection (Nagylaki, 1993; Crow, 2010), and a smaller σ^2_i must be anticipated. However, these results provide new evidence about the relevant role of new mutations on maintaining genetic variability in mammals and must be viewed as an important component affecting the genetic fragility of inbred populations of laboratory species. Although previous authors have suggested that inbred strains cannot be considered as genetically homogeneous (Taft *et al.*, 2006; Stevens *et al.*, 2007; Casellas & Medrano, 2008), the additional contribution of epistatic mutational effects rules out any doubts on the genetic instability of inbred mice, maybe even in some cases impairing reproducibility of research experiments.

The authors are indebted to James F. Crow (University of Wisconsin, Madison, WI) for his helpful comments on this manuscript.

5. Financial support

This work was partially supported by NIH grant DK69978. The research contract of J. Casellas was partially financed by Spain's Ministerio de Ciencia e Innovación (program Ramón y Cajal).

6. Declaration of interest

None.

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