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Estimation of genetic variance components including mutation and epistasis using Bayesian approach in a selection experiment on body weight in mice

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ABSTRACT: Selection experiment was performed for body weight gain in 13 generations of outbred mice. A total of 18 lines were included in the experiment. Nine lines were allotted to each of the two treatment diets containing standard and severely reduced protein level (19.3 and 5.1 % crude protein respectively). Within each diet three lines were selected upwards, three lines were selected downwards and the other three lines were kept as controls. Bayesian statistical methods are used to estimate the genetic variance components. Mixed model analysis is modified including mutation effect following the methods introduced by Wray (1990). DIC was used to compare the model fit. Models with mutation effect have better fit compared to the model with only additive genetic effect. Mutation as direct effect contributes 3.18% of the total phenotypic variance. While in the model with interactions between additive and mutation, it contributes 1.43% as direct effect and 1.36% as interaction effect of the total variance.
Key words: selection, mice, genetic variance, mutation, Bayesian.

Introduction

Mutation is expected to contribute to continuous response to long term selection; but less is known about its role in maintaining genetic diversity of complex traits. Rate of mutation per generation across species is low, but its long term contribution to the total phenotypic variance cannot be taken for granted (Lynch, 1998; Houle *et al.*, 1996).

The estimate of mutational genetic variance in animals and plants have been reported by J Casellas, Caja, & Piedrafita, 2010; Peter D Keightley & Hill, 1992; and Houle *et al*, 1996. These experiments tried to accumulate mutation in long term selection experiments on inbred species (Hill, 1982; Keightley and Hill, 1992). Casellas and Medrano (2008) later came up with a less constrained approach. Employing a method by Wray (1990), they include effects of mutation in a linear mixed model. A modified numerator relationship matrix is used to incorporate the effects of mutation. This methodology can be used in populations with more heterogeneous genetic background that the inbreed lines used in the earlier experiments.

We aim to estimate the genetic variances (including variance due to mutation) in a selection experiment on outbred mice and check the model fit it using Deviance Information Criterion (DIC). A linear mixed model is used to get estimates of the genetic variances using Gibbs sampling. The model is then expanded using the method of Wray (1990) to take mutations effects into account. We use Bayesian approach to solve the models (Sorensen and Gianola, 2002).

Materials and methods

The experiment. The data is form and earlier selection experiment in mice. Experimental design and results of early generations are described by Nielsen (1987). Selection was performed for body weight gain in 13 generations of experimental mice. In each generation a line consisted of eight full sib families. Parents for the next generation were chosen within each litter and mating was performed ensuring maximum avoidance of inbreeding. A total of 18 lines were included in the experiment. Nine lines were allotted to each of the two treatment diets containing standard and severely reduced protein level (19.3 and 5.1 % crude protein respectively). Within each diet three lines were selected upwards, three lines were selected downwards and the other three lines were kept as controls. In total we have 9450 animals with phenotype records on body weight gain (gain) and information about the fixed effects. The full pedigree consists of 13207 animals from 21 discrete generations and all animals can be traced back to 10 founder animals.

Statistical analysis. Gain was used as the selection criteria as well as our trait of interest (y). We used mixed model to analyze the data while incorporating all necessary fixed and random effects (b). Random effects of line (l), litter (d), additive genetic (a) and mutation (m) constitute the basic model along with relevant fixed effects, following the structure,

$\mathbf{y = Xb + Z_1l + Z_2d + Z_3a + Z_3m + e}$

The incorporation of mutation effect in the model follows the method by Wray (1990). The estimation of additive genetic variance is involving the additive genetic (co)variance relationship (**A**) matrix (Wright, 1922). Let additive genetic (co)variance matrix including mutation effect hereby called $\boldsymbol{M}\sigma_m^2$. It is defined as

$$\boldsymbol{M}\sigma_m^2 = \sum_{k=1}^{t} \boldsymbol{A_k}\sigma_m^2$$

M is defined by Casellas and Medrano (2008) as numerator relationship matrix adapted to accommodate the occurrence of mutations. In discrete data, t is the number of generation. $\mathbf{A_k}$ is additive genetic (co)variance matrix attributed to mutations in generation k. Mutation effect is assumed to follow a multivariate normal distribution with mean 0 and variance $\boldsymbol{M}\sigma_m^2$.

We built three models in total: model 1 with only additive genetic effect, model 2 with additive and mutational genetic effects and model 3 with additive, mutation and interaction genetic effects (epistasis). Interaction is defined as additive-mutation interaction (h); with a variance $(A\ o\ M)\sigma_h^2$, which is the Hadamard products of A and M. Model fit were compared by Deviance Information Criterion (DIC). Flat priors were used for all variance components and for all fixed effects.

Results and discussion

Experiment was carefully designed ensuring accurate individual records. Mice were kept in a well-controlled laboratory; minimizing the influence of non-designed effects on the phenotype. There are 9450 animals from 15 generations included in the phenotype dataset. Average mice weight gain is 11.632±4.304 grams. Inbreeding coefficient was 0 in the first four generations which including founder and crossing populations. Inbreeding started to arise in generation 5, when number of animal was expanded. It kept increasing until generation 21 where inbreeding coefficient reaches around 30%.

We analyze and compare three models with different genetic variance components. Variance estimates were obtained using Bayesian approach with flat priors, assuming no previous information about the parameters of interest. The knowledge on mutation accumulation through selection experiment using similar setting on an outbred population is very limited, which supported the decision of using flat priors. Lower DIC value refers to a better model fit and a difference of at least 3 points is considered as statistically significant (Casellas and Medrano, 2008; Spiegelhalter *et al.,* 2002). The DIC estimates presented in table 1 show that model 2 with additive and mutation effect fits the data better compared to the model 1 with only additive effect (27070 compared to 27599). The inclusion of mutation effect picked up new variations emerging in each generation which has not been taken into account by the base (additive) effect. Model 3 with additive, mutation and interaction effect performs even better with DIC estimates of 26834. This result proves that the effect of mutation does exist as a component of genetic variance; it appears as a direct effect as well as in a form of interaction with additive effect.

Table 1. Parameter estimates.

Parameters	Model 1	Model 2	Model 3
Line variance	0.210	0.198	0.199
Litter variance	1.529	1.540	1.506
Additive genetic variance	3.430	1.207	1.625
Mutation variance	-	0.252	0.144
Interaction variance	-	-	0.108
Residual variance	5.006	4.724	4.383
Total	10.175	7.921	7.965
DIC	27599	27070	26834

We differentiate the genetic variance component into base population additive genetic variance and new emerged variance in each generation (mutation), base population variance went down 3.430 to 1.207. Even though there is new variance component, which is mutation; its contribution is not comparable to the decrease in the additive genetic variance. Mutational variance is estimated per generation, total genetic variance then becomes a balance between number of generations, loss of variance due to inbreeding and the amount of base population additive variance. Mutational variance per generation contributes 3.15% of the total phenotypic variance in model 2, which agrees with the review of Houle *et al.* (1996) that mutational heritability values in different animal and plants species are around 10^{-4} to 5.10^{-2}. Mutational variance are not necessarily cumulative, not all of them will be passed on to the next generations; some will lost due to inbreeding and random drift.

Model 3 incorporates the possible effect of interactions between mutations as another genetic variance component of interest. This model results in a new division of genetic variance components: additive effect takes into account 20.4% of the total variance, whereas mutation and interaction effects are 1.43 and 1.36% respectively. Considering that genes act together in a network to produce a trait which is often called polygenes (Mackay, 2001), the presence of mutated genes could exhibit multiple effects, both direct and as interactions with other genes.

Conclusions

- Models including mutation effect perform better than model with only additive effect.
- In long term selection experiment, mutational variance is in the range of 1.43 to 3.18% of phenotypic variance per generation.
- This mutational variance is not necessarily cumulative across generations. Some of them will be lost due to inbreeding and drift.
- The effect of mutation also present in the form of interactions between additive effect and mutation in current generation.

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