Change in maternal environment induced by cross-fostering alters genetic and epigenetic effects on complex traits in mice

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The interaction between maternally provided environment and offspring genotype is a major determinant of offspring development and fitness in many organisms. Recent research has demonstrated that not only genetic effects, but also epigenetic effects may be subject to modifications by the maternal environment. Genomic imprinting resulting in parent-of-origin-dependent gene expression is among the best studied of epigenetic effects. However, very little is known about the degree to which genomic imprinting effects can be modulated by the maternally provided environment, which has important implications for phenotypic plasticity. In this study, we investigated this unresolved question using a cross-fostering design in which mouse pups were nursed by either their own or an unrelated mother. We scanned the entire genome to search for quantitative trait loci whose effects depend on cross-fostering and detected 10 of such loci. Of the 10 loci, 4 showed imprinting by cross-foster interactions. In most cases, the interaction effect was due to the presence of an effect in either cross-fostered or non-cross-fostered animals. Our results demonstrate that genomic imprinting effects may often be modified by the maternal environment and that such interactions can impact key fitness-related traits suggesting a greater plasticity of genomic imprinting than previously assumed.

Keywords: cross-fostering; genomic imprinting; maternal environment; QTL; phenotypic plasticity; mice

1. INTRODUCTION

Phenotypic variation in quantitative traits reflects both genetic and environmental influences and, quite often, the interaction between the two (e.g. Kafkafi *et al.* 2005; Mackay & Anholt 2007). The extent of such genotype-by-environment interactions is variable and depends on the trait in question as well as the organism, but in many organisms these interactions can explain a major component of phenotypic variance (e.g. Gutteling *et al.* 2007). Such effects can arise not only from interactions with the general ‘ecological’ environment, but may also arise from interactions with the social environment provided by conspecifics (e.g. Eklund 1997; Wolf 2000; Hager & Johnstone 2006a). In most mammals, a major component of the social environment is provided by mothers and this maternally provided environment has been shown to be a major determinant of offspring phenotype through both behaviour and provisioning (Maestripieri & Mateo 2009). Because such maternal effects can account for a relatively large proportion of phenotypic variance (Roff 1997), many studies wish to control for such effects to obtain estimates of the independent effects of offspring and maternal genotype on offspring trait variation (Cowley *et al.* 1989; Lock *et al.* 2004). However, since the maternal and offspring genotypes are correlated due to relatedness, it can often be difficult to achieve such a clean separation. As a result, laboratory and field studies have used cross-fostering, where an unrelated female cares for the young of a

different female, to remove the confounding correlation caused by relatedness (e.g. Ressler 1962; Hager & Johnstone 2003; Mateo & Holmes 2004; Kruuk & Hadfield 2007). In the fields of behavioural ecology and animal behaviour, cross-fostering has been widely used in taxa ranging from insects to birds and mammals, for example to study kin recognition (Aldhous 1989; Penn & Potts 1998), or the separate influences of parent and offspring on provisioning and offspring weight or behaviour (Huck & Banks 1980; Hager & Johnstone 2006b, 2007).

Of particular interest is the question of whether epigenetic effects, such as genomic imprinting, can depend on the maternally provided environment, as this would suggest an epigenetic mechanism through which individuals could flexibly respond to environmental changes. Briefly, genomic imprinting refers to parent-of-origin-dependent gene expression, where the paternally and maternally inherited alleles are expressed to different degrees (Hayward *et al.* 1998; Reik & Walter 2001). This epigenetic effect is primarily caused by differential methylation of the two alleles although histone modifications and microRNA may also modify allele-specific expression (Wilkinson *et al.* 2007; Seitz *et al.* 2008). In quantitative genetics analyses, the phenotypic effects of imprinting can be detected by distinguishing the two heterozygotes that may show different phenotypes depending on the parent-of-origin of their alleles (Cheverud *et al.* 2008; Wolf *et al.* 2008a). To our knowledge, only one study has demonstrated to date that the epigenetic status of a particular gene (the glucocorticoid receptor promoter) can be altered depending on the maternal environment (Weaver *et al.* 2004). The exciting possibility

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that such reprogramming may be possible for other loci that affect different complex and fitness-related traits has, however, not been explored.

In this study, we set out to analyse whether the effects of offspring genotype on offspring phenotype depend on the nature of the maternally provided environment. We alter maternal environment by cross-fostering such that cross-fostered pups are reared by unrelated mothers. Using a quantitative trait locus (QTL) mapping approach in a population of mice in which half-litters were cross-fostered at birth, we investigated specifically whether the additive genetic, dominance or genomic imprinting effects of a locus on bodyweight and growth may vary as a result of the change in maternal environment through cross-fostering. With this analysis, we then determined how allelic variation at a locus can result in differences in phenotypes in cross-fostered versus non-cross-fostered animals.

2. METHODS

The study population consisted of the F_2 and F_3 generations of an intercross between the inbred mouse strains Large (LG/J) and Small (SM/J). The population was initiated by mating 10 males of the SM/J strain to 10 females of the LG/J strain resulting in the F_1 population of 52 individuals. These F_1 individuals were randomly mated to produce 510 F_2 animals and random mating among F_2 animals yielded 200 full-sib families of the F_3 generation with a total of 1632 individuals. Half-litters were reciprocally cross-fostered between litters born on the same day for 158 of the 200 F_3 litters (Kramer *et al.* 1998). We analysed weekly weight from week 1 to week 10 and two growth periods: preweaning growth from weeks 1 to 3 and postweaning growth from weeks 3 to 10.

Details on the genotyping of mice are given in Wolf *et al.* (2008b) and only briefly described here. Our dataset is composed of 353 SNP marker genotypes for each animal, evenly placed throughout the genome, except for regions in which LG/J and SM/J have been found to be monomorphic (Hrbek *et al.* 2006). Haplotypes were reconstructed with the program Pedphase using the integer linear programming algorithm (Li & Jiang 2005) to produce a set of unordered haplotypes for the F_2 generation and a set of ordered haplotypes (ordered by parent-of-origin of alleles) for the F_3 generation. Throughout we designate the four ordered genotypes as *LL*, *LS*, *SL* and *SS*, with the *L* allele originating from the LG/J strain and the *S* allele from the SM/J strain (paternal/maternal allele).

We assigned the four ordered genotypes at the marker loci additive (*a*), dominance (*d*) and parent-of-origin (*i*) genotypic index scores following Mantey *et al.* (2005), as adapted in Wolf *et al.* (2008b). The interactions between these three effects and cross-fostering status provide a set of independent tests of whether the change in the effect of the locus is attributable to a change in the additive, dominance or imprinting effect (or some combination of the three). To identify loci that showed a significant interaction effect with cross-fostering status, we fitted a mixed model with the main effects of cross-fostering and genotype (X_{fost} , *a*, *d*, *i*) as well as the interaction between the two ($X_{fost} \times a$, $X_{fost} \times d$, $X_{fost} \times i$), and biological and foster family (*dam*, *nurse*) as random effect class variables using maximum likelihood as implemented in the Mixed Procedure of SAS (SAS version 9.1; SAS Institute, Cary, NC, USA). This model was used to scan the genome to produce a probability distribution

for the overall effect of the locus as well as the interaction effects. The probability was generated by comparing the $-2 \log$ likelihood computed by SAS for the model with the fixed genetic effects and their interactions to a reduced model that did not include these six effects. The difference in the $-2 \log$ likelihoods of the two models is χ^2 distributed with six degrees of freedom (since the two models differ by six fixed effects representing a total of six degrees of freedom). These probability values were then transformed to a log probability ratio (LPR) in order to make them comparable to the LOD scores commonly seen in QTL analyses ($LPR = -\log_{10}[\text{probability}]$).

We identified significant loci whose LPR value exceeded the genome-wide threshold for the overall locus test and that showed a significant interaction effect. In two cases, the interaction effect, but not the overall locus effect, exceeded the genome-wide threshold and we have thus included these loci here (*Xf4.1* and *Xf10.1*). The significance testing was based on the effective number of markers method based on the eigenvalues of the marker correlation matrix (Li & Ji 2005). This method allows for direct computation of the thresholds for all traits and calculates the number of independent tests in a genome or chromosome scan using the effective number of markers in a Bonferroni correction. After loci were identified using the genome-wide significance thresholds, we determined potential pleiotropic effects of loci in a protected test where all effects of QTL are included whenever the effect of a locus on other traits is significant at the pointwise ($p < 0.05$; $LPR > 1.3$) level. We characterized the nature of interactions using a set of orthogonal contrasts corresponding to additive, dominance and imprinting effects.

We distinguish a total of three different imprinting patterns: parental (paternal or maternal) expression, bipolar dominance and polar dominance. Maternal or paternal expression occurs when those individuals sharing the same maternal or paternal allele have the same average phenotype. Bipolar imprinting refers to the case where the two homozygotes have the same average phenotypes, but the reciprocal heterozygotes are significantly different from each other. Finally, polar dominance describes cases where one of the two heterozygotes is different (either larger or smaller) from all three other genotypes (Wolf *et al.* 2008b).

The appearance of parent-of-origin-dependent effects on offspring phenotypes may be caused by either maternal genetic effects or genomic imprinting (Hager *et al.* 2008), as can the appearance of additive effects because of the genetic autocorrelation of offspring with their parents at a locus (where, at a particular locus, the correlation is 1/2). In other words, the locus is expressed in the mother and affects the phenotype of her offspring, but they then inherit an allele from her that makes it appear as if that locus directly affects their own phenotype (when it may not). This phenomenon is relevant to cross-fostering effects since postnatal maternal effects would only result in the appearance of a direct effect in the non-cross-fostered offspring as the postnatal maternal-offspring genetic correlation is broken by cross-fostering. Therefore, we tested all loci with a significant cross-foster interaction effect to determine whether the interaction effect could be explained by a maternal genetic effect or was indeed associated with a change in the direct effect of a locus. This was achieved by analysing whether the parent-of-origin-dependent effect or additive effect differed between individuals reared by homozygous versus heterozygous mothers. A true additive or imprinting-by-cross-foster effect

should appear regardless of the type of mother, while an effect caused by a maternal effect should only appear in the class in which individuals had homozygous mothers. Since maternal effects do not contribute to differences among heterozygous offspring (i.e. there is no genetic variation among heterozygous mothers at the locus in question), the appearance of an imprinting effect cannot be attributed to a maternal effect.

3. RESULTS

Our analysis of cross-fostering interactions with genotype detected a total of ten QTL on seven chromosomes. All loci showed a significant interaction with only one of the three genetic effects (additive, dominance or imprinting) and a significant effect occurred in either cross-fostered or non-cross-fostered (table 1). However, two loci were characterized by significant effects in both groups where the effects were different in magnitude (thus causing the interaction). We refer to these QTL as $Xf_{y,z}$, where Xf stands for 'cross-fostering'. This is followed by the chromosome number (1–19) and the number of the QTL on that particular chromosome in case several loci would be identified on the same chromosome. All loci showed pleiotropic effects where more than one trait was affected, ranging from three affected traits ($Xf1.3$) to eight ($Xf10.1$). Furthermore, all loci showed significant main effects at the genome-wide level except two loci that exhibited genome-wide significant interactions. Three of the loci detected here ($Xf1.1$, $Xf7.1$ and $Xf14.1$) confirm previously found loci with significant main imprinting effects (cf. Wolf *et al.* 2008b).

(a) Differences between cross-fostered and non-cross-fostered individuals

The key result of our study focuses on the differences in the genetic effects between cross-fostered and non-cross-fostered animals. As shown in table 1, the separate effects need not necessarily be significant in the two individual groups although the difference in effects between the two is. This also explains that the sign of effect in cross-fostered and non-cross-fostered animals may be the same (e.g. $Xf6.1$). More common is the pattern that a locus may exert a positive effect in one group and a negative effect in the other (e.g. $Xf10.1$, $Xf14.1$). Beginning with the two loci that show a significant interaction between additive effects and cross-fostering only ($Xf6.1$ and $Xf10.2$), we see in table 1 that estimates for additive effects were positive for both groups (except growth 13) suggesting that while *LL* homozygotes were always larger than *SS* homozygotes, the former were significantly larger in cross-fostered than in non-cross-fostered animals. We confirmed in the maternal effects analysis that all additive effect interactions are indeed interactions of direct effects with cross-fostering.

Of the ten loci discovered, four showed imprinting by cross-foster interactions (one locus on distal chromosome 7 where the parent-of-origin-dependent effect was caused by maternal genetic effects is not discussed here). While not restricted to a specific period in development, these interactions were characterized by a significant imprinting effect in cross-fostered animals (table 1) with one exception ($Xf7.1$). A good example illustrating the imprinting interaction effect is given in figure 1 for week 5 bodyweight at $Xf10.1$. It can be seen that in cross-fostered animals

maternal expression occurs, whereas in non-cross-fostered animals a paternal expression pattern appears, bearing in mind that in the latter group the imprinting effect alone just misses significance ($p = 0.061$). Importantly, our results suggest that the imprinting effect at these loci depends on the differences experienced in the specific environments of the two groups of animals.

Looking at the proportion of phenotypic variance explained, we found that loci with significant interactions explained a moderate proportion of phenotypic variance in the trait concerned (table 1), with the interaction effect accounting for between less than 1 per cent to 2.7 per cent of the phenotypic variance with imprinting interactions explaining the highest proportion of variance followed by additive and dominance interactions. Yet, for a given trait the r^2 value for the sum of the significant interaction effects of the loci reached up to 10.3 per cent of phenotypic variation at week 5.

4. DISCUSSION

To our knowledge, the work presented here is the first study using a QTL approach demonstrating that cross-fostering can influence the impact of additive, dominance and genomic imprinting effects on complex trait expression resulting in differences between cross-fostered and non-cross-fostered animals both in terms of number of effects and their magnitude. While individual interactions have comparatively small effects, their cumulative effect can be considerable. This highlights the importance of genotype by environment interactions for trait variation in general, and for studies on development in particular, and may identify locations in the genome in which genes are more susceptible to environmental perturbations. Of particular interest is the result that epigenetic effects caused by genomic imprinting can interact with the environment provided by mothers. Certainly, this finding suggests an additional level of complexity by which epigenetic effects may operate to affect phenotypes and requires further investigation into underlying mechanisms and sources other than maternal environment that contribute to differences in environment due to cross-fostering.

Although results of many studies have shown the existence of environmental interaction effects with genotype (Ressler 1962; Francis *et al.* 2003; Bartolomucci *et al.* 2004), the importance of such effects for trait variation and evolution has only recently been highlighted by research, showing that they can have transgenerational effects. For example, Francis *et al.* (1999) demonstrated in a cross-foster experiment in rats that maternal behaviour impacts stress responses in offspring and that differences caused in this parameter were transmitted to females in the next generation. Several underlying mechanisms are conceivable for transgenerational effects, but a particularly arresting possibility involves epigenetic reprogramming. In a landmark paper, Weaver *et al.* (2004) investigated how an epigenetic effect such as maternal behaviour may affect the methylation status of the glucocorticoid receptor in the brain of young mice. This study demonstrated that methylation levels were influenced depending on the behaviour of their respective foster mothers and that the altered methylation status of the receptor persisted into adulthood.

Table 1. Cross-foster interaction QTL. The first column identifies the QTL followed by the genomic location (Locat.) in F₂ equivalent centiMorgans (cM) and the coordinates (Coord.) in megabases based on mouse genome build 36. 'mLPR' lists the overall LPR for the test of main effects and interaction effects followed by the trait affected. We then describe the interaction effect for cross-fostered (*Xf*) and non-cross-fostered (non-*Xf*) individuals. We list the type and sign of the effect in the two sets of individuals where 'a' refers to additive, 'd' to dominance and 'i' to imprinting effects. For example, '-a' under *Xf* refers to the case of a negative additive effect in cross-fostered individuals. Effects in bold indicate significance of that effect in the particular group (*Xf* or non-*Xf*). The column headed 'test' gives the LPR for the interaction effect alone and under '*r*²', we give the proportion of phenotypic variance explained by the interaction effect (i.e. it does not include the main effect of the locus).

QTL	Locat.	Coord.	mLPR	trait	interaction effect		test	<i>r</i> ²
					<i>Xf</i>	non- <i>Xf</i>		
<i>Xf1.1</i>	0	3.16	2.16	Week 2	+ <i>i</i>	- <i>i</i>	1.56	0.85
			4.33	Week 3	+<i>i</i>	- <i>i</i>	2.61	1.44
			5.48	Week 4	+<i>d</i>	- <i>d</i>	1.3	0.65
			4.88	Week 5	+<i>d</i>	- <i>d</i>	1.68	0.96
			4.80	Week 6	+<i>d</i>	- <i>d</i>	1.72	0.99
			3.99	Grow 13	+ <i>i</i>	- <i>i</i>	2.03	1.34
<i>Xf1.2</i>	31.79	68.8	4.20	Week 3	+<i>d</i>	+ <i>d</i>	1.51	0.61
			2.93	Week 4	+<i>d</i>	+ <i>d</i>	1.56	0.83
			3.10	Week 5	+<i>d</i>	+ <i>d</i>	1.78	1.04
			2.49	Week 6	+<i>d</i>	+ <i>d</i>	2.03	1.04
			2.39	Week 7	+<i>d</i>	+ <i>d</i>	1.56	0.90
<i>Xf1.3</i>	55.89	144.5	4.51	Week 3	+<i>d</i>	+ <i>d</i>	1.85	0.80
			2.07	Week 4	+<i>d</i>	- <i>d</i>	2.54	1.53
			4.24	Grow 13	+<i>d</i>	- <i>d</i>	1.31	0.66
<i>Xf4.1</i>	37.28	84.3	3.06	Week 1	+<i>d</i>	- <i>d</i>	4.13	2.13
			2.69	Week 2	+<i>d</i>	+ <i>d</i>	1.62	0.70
			3.37	Week 3	+<i>d</i>	+ <i>d</i>	2.44	1.05
			2.46	Week 4	+<i>d</i>	+ <i>d</i>	1.72	0.89
<i>Xf6.1</i>	38.73	90.1	1.72	Week 2	+<i>a</i>	+ <i>a</i>	1.37	0.63
			2.05	Week 3	+<i>a</i>	+ <i>a</i>	1.81	0.81
			5.54	Week 4	+<i>a</i>	+<i>a</i>	2.07	1.21
			7.39	Week 5	+<i>a</i>	+<i>a</i>	2.90	1.87
			8.78	Week 6	+<i>a</i>	+<i>a</i>	1.96	1.15
			10.17	Week 7	+<i>a</i>	+<i>a</i>	2.22	1.37
			10.86	Week 8	+<i>a</i>	+<i>a</i>	1.50	0.86
<i>Xf7.1</i>	27.70	56.3	2.36	Grow 13	+<i>a</i>	- <i>a</i>	2.70	1.68
			4.49	Week 3	- <i>i</i>	+ <i>i</i>	1.43	0.58
			4.18	Week 4	- <i>i</i>	+ <i>i</i>	1.33	0.68
			11.89	Week 5	+ <i>i</i>	+<i>i</i>	2.05	1.22
			15.95	Week 6	+ <i>i</i>	+<i>i</i>	2.20	1.31
			14.37	Week 7	+ <i>i</i>	+<i>i</i>	1.88	1.11
			12.26	Week 8	+ <i>i</i>	+<i>i</i>	1.33	0.76
			3.58	Grow 13	+ <i>i</i>	+<i>i</i>	1.46	0.76
<i>Xf8.1</i>	35.84	60.27	2.19	Week 3	+<i>i</i>	- <i>i</i>	1.34	0.60
			2.66	Week 4	+<i>a</i>	+ <i>a</i>	1.47	0.85
			4.42	Week 5	+<i>a</i>	+ <i>a</i>	1.32	0.68
			5.06	Week 6	+<i>a</i>	+<i>a</i>	1.85	1.10
			4.71	Week 7	+<i>a</i>	+ <i>a</i>	1.56	0.90
<i>Xf10.1</i>	0	16.0	0.75	Week 3	+ <i>i</i>	- <i>i</i>	1.56	0.80
			1.18	Week 4	+ <i>i</i>	- <i>i</i>	2.31	1.62
			1.99	Week 5	+<i>i</i>	- <i>i</i>	3.49	2.68
			1.65	Week 6	+<i>i</i>	- <i>i</i>	3.28	2.47
			1.92	Week 7	+<i>i</i>	- <i>i</i>	2.58	1.87
			1.76	Week 8	+<i>i</i>	- <i>i</i>	1.77	1.21
			1.54	Week 9	+<i>i</i>	+ <i>i</i>	1.46	0.93
			2.07	Week 10	+<i>i</i>	+ <i>i</i>	1.81	1.23
<i>Xf10.2</i>	46.26	105.4	2.57	Week 4	+<i>a</i>	+ <i>a</i>	1.47	0.91
			4.12	Week 5	+<i>a</i>	+ <i>a</i>	1.46	0.91
			4.18	Week 6	+<i>a</i>	+ <i>a</i>	1.47	0.91
			2.37	Grow 13	+<i>a</i>	- <i>a</i>	1.76	1.16
<i>Xf14.1</i>	37.75	81.2	3.91	Week 5	- <i>d</i>	+<i>d</i>	1.65	0.97
			5.16	Week 6	- <i>d</i>	+ <i>d</i>	1.83	1.11
			5.94	Week 7	- <i>d</i>	+ <i>d</i>	1.73	1.04
			4.71	Week 9	- <i>d</i>	+ <i>d</i>	1.40	0.81
			3.90	Week 10	- <i>d</i>	+ <i>d</i>	1.60	0.97

Figure 1. Changes in effects of loci associated with cross-fostering. Imprinting by cross-fostering interaction for week 5 body weight at *Xf10.1*. In black are given the phenotypic values for cross-fostered animals while the white bars refer to non-cross-fostered animals; the first allele of a genotype is paternally derived and the second is maternally derived. Shown are the mean trait values with their standard errors (SE).

Using a different approach, our results lend further support to the notion that epigenetic effects caused by genomic imprinting can be modulated by the social environment, particularly that provided by mothers. We were able to demonstrate that such interactions may occur at different locations across the genome where no overall significant main imprinting effect has been detected (cf. Wolf *et al.* 2008b) and where the interaction effect accounted for most of the locus effect. These results suggest that more imprinted loci show flexibility (possibly in their underlying mechanism of differential methylation) than one may have assumed from previous work and that variation in a wide range of complex traits, including those related to diseases, could be affected. However, how a change in methylation status would be effected remains unclear at present and presents a challenge for future research.

As cross-fostering removes the relatedness between mother and offspring for adoptive litters, several potential mechanisms could underlie the observed changes in general. We note that although there is the potential that sibling (or, generally, littermate) social environments could also be important, they are unlikely to play a role in the effects we detected here. This is because cross-fostering was reciprocal, such that individuals in both litters of a cross-fostered pair experienced the same average sibling social environment, and therefore there is generally no difference in this environment experienced by cross-fostered and non-cross-fostered groups. Given the results of Weaver *et al.* (2004), it seems likely that behavioural changes play an important role here. For example, Hager & Johnstone (2005) found differential growth of own and alien pups in a mixed litter, which could be due to preferential nursing or retrieval of own pups by mothers (e.g. Yamazaki *et al.* 2000). Alternatively, pups nursed by unrelated mothers may be less effective in solicitation behaviour and separation from the cage in which pups are born may result in a 'home-cage advantage' of pups reared by their own mothers. Any of these pathways could conceivably play a role in the observed effect change on bodyweight in this study, but without direct observation it seems rather difficult to go beyond mere speculation at this stage.

We have demonstrated that phenotypic plasticity (i.e. the ability of individuals to respond to environmental clues, e.g. West-Eberhard 2003) does not only stem from flexible genetic effects (additive and dominance), but may also extend to epigenetic effects such as genomic imprinting. Indeed, our results suggest that epigenetic effects are likely to be affected by changes, particularly in the maternal environment. Whether or not this flexibility demonstrated here confers adaptive advantages remains to be tested.

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REFERENCES

- Aldhous, P. 1989 The effects of individual cross-fostering on the development of intrasexual kin discrimination in male laboratory mice, *Mus musculus* L. *Anim. Behav.* **37**, 741–750. (doi:10.1016/0003-3472(89)90060-2)
- Bartolomucci, A., Gioiosa, L., Chirieleison, A., Ceresini, G., Parmigiani, S. & Palanza, P. 2004 Cross fostering in mice: behavioral and physiological carry-over effects in adulthood. *Genes Brain Behav.* **3**, 115–122. (doi:10.1111/j.1601-183X.2003.00059.x)
- Cheverud, J. M., Hager, R., Roseman, C., Fawcett, G., Wang, B. & Wolf, J. B. 2008 Genomic imprinting effects on adult body composition in mice. *Proc. Natl Acad. Sci. USA* **105**, 4253–4258. (doi:10.1073/pnas.0706562105)
- Cowley, D., Pomp, D., Atchley, W. R., Eisen, E. J. & Hawkins-Brown, D. 1989 The impact of maternal uterine genotype on postnatal growth and adult body size in mice. *Genetics* **122**, 193–203.
- Eklund, A. 1997 The effect of early experience on MHC based mate preferences in two B10.W strains of mice (*Mus domesticus*). *Behav. Genet.* **27**, 223–229. (doi:10.1023/A:1025658013443)
- Francis, D., Diorio, J., Liu, D. & Meaney, M. J. 1999 Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science* **286**, 1155–1158. (doi:10.1126/science.286.5442.1155)
- Francis, D. D., Szegda, D., Campbell, K., Martin, G. & Insel, W. D. 2003 Epigenetic sources of behavioural differences in mice. *Nat. Neurosci.* **6**, 445–448. (doi:10.1038/nm1038)
- Gutteling, E. W., Riksen, J. A. G., Bakker, J. & Kammenga, J. E. 2007 Mapping phenotypic plasticity and genotype–environment interactions affecting life-history traits in *Caenorhabditis elegans*. *Heredity* **98**, 28–37. (doi:10.1038/sj.hdy.6800894)
- Hager, R. & Johnstone, R. A. 2003 The genetic basis of family conflict resolution in mice. *Nature* **421**, 533–535. (doi:10.1038/nature01239)
- Hager, R. & Johnstone, R. A. 2005 Differential growth of own and alien young in mixed litters of mice: a role for genomic imprinting. *Ethology* **111**, 705–711. (doi:10.1111/j.1439-0310.2005.01097.x)
- Hager, R. & Johnstone, R. A. 2006a The influence of phenotypic and genetic effects on maternal provisioning and offspring weight gain in mice. *Biol. Lett.* **2**, 81–84. (doi:10.1098/rsbl.2005.0403)
- Hager, R. & Johnstone, R. A. 2006b Early experience and parent-of-origin-specific effects influence female reproductive success in mice. *Biol. Lett.* **2**, 253–256. (doi:10.1098/rsbl.2006.0457)
- Hager, R. & Johnstone, R. A. 2007 Maternal and offspring effects influence maternal provisioning to mixed litters

- of own and alien young in mice. *Anim. Behav.* **74**, 1055–1059.
- Hager, R., Cheverud, J. M. & Wolf, J. B. 2008 Maternal effects as the cause of parent-of-origin-dependent effects that mimic genomic imprinting. *Genetics* **178**, 1755–1762. (doi:10.1534/genetics.107.080697)
- Hayward, B. E., Moran, V., Strain, L. & Bonthron, D. T. 1998 Bidirectional imprinting of a single gene: GNAS1 encodes maternally, paternally and biallelically derived proteins. *Proc. Natl Acad. Sci. USA* **95**, 15 474–15 480.
- Hrbek, T., de Brito, R. A., Wang, B., Pletscher, L. S. & Cheverud, J. M. 2006 Genetic characterization of a new set of recombinant inbred lines (LGXSM) formed from the intercross of SM/J and LG/J inbred mouse strains. *Mamm. Genome* **17**, 417–429. (doi:10.1007/s00335-005-0038-7)
- Huck, U. W. & Banks, E. M. 1980 The effects of cross-fostering on the behaviour of two species of North American lemmings, *Dicrostonyx groenlandicus* and *Lemmus trimucronatus*. *Behaviour* **73**, 261–275. (doi:10.1163/156853980X00267)
- Kafkafi, N., Benjamini, Y., Sakov, A., Elmer, G. I. & Golani, I. 2005 Genotype–environment interactions in mouse behavior: a way out of the problem. *Proc. Natl Acad. Sci. USA* **102**, 4619–4624. (doi:10.1073/pnas.0409554102)
- Kramer, M. G., Vaughn, T. T., Pletscher, L. S., King-Ellison, K., Adams, E. & Cheverud, J. M. 1998 Genetic variation for body weight gain and composition in the intercross of Large (LG/J) and Small (SM/J) inbred strains of mice. *Genet. Mol. Biol.* **21**, 211–218.
- Kruuk, L. E. B. & Hadfield, J. D. 2007 How to separate genetic and environmental causes of similarity between relatives. *J. Evol. Biol.* **20**, 1890–1903. (doi:10.1111/j.1420-9101.2007.01377.x)
- Li, J. & Ji, L. 2005 Adjusting multiple testing in multilocus analyses using the eigenvalues of a correlation matrix. *Heredity* **95**, 221–227. (doi:10.1038/sj.hdy.6800717)
- Li, J. & Jiang, T. 2005 Computing the minimum recombinant haplotype configuration from incomplete genotype data on a pedigree by integer linear programming. *J. Comp. Biol.* **12**, 719–739. (doi:10.1089/cmb.2005.12.719)
- Lock, J. E., Smiseth, P. R. & Moore, A. J. 2004 Selection, inheritance, and the evolution of parent–offspring interactions. *Am. Nat.* **164**, 13–24. (doi:10.1086/421444)
- Mackay, T. F. C. & Anholt, R. R. H. 2007 Ain't misbehavin'? Genotype–environment interactions and the genetics of behavior. *Trends Genet.* **23**, 311–314. (doi:10.1016/j.tig.2007.03.013)
- Maestripietri, D. & Mateo, J. M. 2009 *Maternal effects in mammals*. Chicago, IL: University of Chicago Press.
- Mantey, C., Brockmann, G. A., Kalm, E. & Reinsch, N. 2005 Mapping and exclusion mapping of genomic imprinting effects in mouse F2 families. *J. Hered.* **96**, 329–338. (doi:10.1093/jhered/esi044)
- Mateo, J. M. & Holmes, W. G. 2004 Cross-fostering as a means to study kin recognition. *Anim. Behav.* **68**, 1451–1459. (doi:10.1016/j.anbehav.2004.01.017)
- Penn, D. J. & Potts, W. K. 1998 MHC-disassortative mating preferences reversed by cross-fostering. *Proc. R. Soc. B* **265**, 1299–1306.
- Reik, W. & Walter, J. 2001 Genomic imprinting: parental influence on the genome. *Nat. Rev.* **2**, 21–32.
- Ressler, R. H. 1962 Parental handling in two strains of mice reared by foster parents. *Science* **137**, 129–130. (doi:10.1126/science.137.3524.129)
- Roff, D. A. 1997 *Evolutionary quantitative genetics*. New York, NY: Chapman and Hall.
- Seitz, H., Royo, H., Bortolin, M., Lin, S. P. & Ferguson-Smith, A. C. 2008 A large imprinted microRNA gene cluster at the mouse Dlk1–Gtl2 domain. *Genome Res.* **14**, 1741–1748. (doi:10.1101/gr.2743304)
- Weaver, I. C. G., Cervoni, N., Champagne, F. A., D'Alessio, A. C. D., Sharma, S., Seckl, R. S., Dymov, S., Szyf, M. & Meaney, M. 2004 Epigenetic programming by maternal behavior. *Nat. Neurosci.* **7**, 847–854. (doi:10.1038/nn1276)
- West-Eberhard, M. J. 2003 *Developmental plasticity and evolution*. New York, NY: Oxford University Press.
- Wilkinson, L. S., Davies, W. & Isles, A. R. 2007 Genomic imprinting effects on brain development and function. *Nat. Rev. Neurosci.* **8**, 832–843. (doi:10.1038/nrn2235)
- Wolf, J. B. 2000 Gene interactions from maternal effects. *Evolution* **54**, 1882–1898.
- Wolf, J. B., Hager, R. & Cheverud, J. M. 2008a Genomic imprinting effects on complex traits: a phenotype-based perspective. *Epigenetics* **3**, 295–299.
- Wolf, J. B., Cheverud, J. M., Roseman, C. & Hager, R. 2008b Genome-wide analysis reveals a complex pattern of genomic imprinting in mice. *PLoS Genet.* **4**, e1000091. (doi:10.1371/journal.pgen.1000091)
- Yamazaki, K., Beauchamp, G. K., Curran, M., Bard, J. & Boyse, E. A. 2000 Parent–progeny recognition as a function of MHC odortype identity. *Proc. Natl Acad. Sci. USA* **97**, 10 500–10 502. (doi:10.1073/pnas.180320997)