Comparative architectures of direct and social genetic effects from the genome-wide association study of 170 phenotypes in outbred laboratory mice

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Abstract

Social genetic effects (SGE, also called indirect genetic effects) are associations between genotypes of one individual and phenotype of another. SGE can arise when two individuals interact and heritable traits of one individual influence the phenotype of the other. To better understand the architecture of SGE, we re-analysed an existing dataset comprising 170 behavioural, physiological and morphological phenotypes measured in outbred laboratory mice. For all phenotypes and in order to compare SGE with better-known direct genetic effects (DGE, associations between an individual's genotypes and their own phenotype), we analysed polygenic models with random terms for SGE and DGE and performed the genome-wide association study of both SGE (sgeGWAS) and DGE (dgeGWAS). Our analyses yielded two main insights: first, SGE and DGE *acting on the same phenotype* generally arise from partially different loci and/or loci with different effect sizes; secondly, individual SGE associations typically explain less phenotypic variance than DGE associations. Our results shed light on the architecture of SGE and have important implications for the design of future studies. Importantly, we detail and validate methods that can be used for sgeGWAS

in outbred populations with any levels of relatedness and group sizes, and provide software to perform these analyses.

Main text

Introduction

Social interactions between two individuals can result in the phenotype of one individual being affected by genotypes of their social partner. Such effects arise when heritable traits of the social partner influence the phenotype of interest (Figure 1a), and are called indirect genetic effects or social genetic effects[1-4] (SGE).

SGE have been shown to contribute significantly and substantially to phenotypic variation in livestock, wild animals, plants and laboratory model organisms (see review by Bijma[5] and subsequent references). In laboratory mice, SGE have been found to affect a broad range of phenotypes including behavioural, physiological, and morphological traits[6-9], and in humans effects of non-transmitted parental alleles have been detected on offspring's educational attainment[10-12]. Thus, SGE are an important component of the genotype to phenotype path, and understanding their architecture is important.

SGE can be used as a tool to identify traits of social partners affecting a phenotype of interest. For example, a candidate gene study of SGE on plumage condition in laying hens[13] found an indirect association with the serotonin receptor 2C gene. As the serotoninergic system is known to control behaviour, this SGE association is consistent with observations of cage mates influencing the plumage of a focal hen through feather pecking. When traits of social partners affecting the phenotype of interest are unknown, the genome-wide association study of SGE (sgeGWAS) may be a promising avenue. Indeed, similarly to how GWAS of "traditional" direct genetic effects (DGE, effects of an individual's genotypes on its own phenotype) has provided valuable insights into the "within-body" pathways affecting disease and quantitative phenotypes[14], sgeGWAS could help dissect the "between-bodies" pathways of social effects and provide clues on the traits of social partners

that mediate social effects. Deploying sgeGWAS reliably and efficiently will however require a good understanding of the architecture of SGE.

Information on the architecture of SGE is relatively sparse, as few studies have identified genomic loci that influence phenotypes of social partners. Quasi-Mendelian SGE exist[15,16] but candidate gene studies and GWAS of SGE have revealed oligo- or polygenic architectures for a larger number of phenotypes[7,8,13,17,18]. Two key features of such complex architectures are the degree of overlap between SGE and DGE loci, and the proportion of variance explained by SGE loci. The degree of overlap between SGE and DGE has most often been studied in terms of the genome-wide correlation between SGE and DGE effect sizes, and it has been shown to be an important determinant of the response of a phenotype to selection[19-24]. In addition, whether the strongest SGE and DGE for any given phenotype arise from the same loci is of practical interest: it determines how redundant sgeGWAS may be with dgeGWAS of the same phenotype and whether loci identified in dgeGWAS may also have effects on the same phenotype of partners.

Similarly, the variance explained by individual SGE loci is both of fundamental and practical interest, as it provides insights into the evolutionary process and determines the power of sgeGWAS. Estimates of the variance explained by individual SGE loci are most informative when similar estimates for DGE loci acting on the same phenotype and in the same population are available for comparison. Of the few studies that have mapped SGE[7,8,13,17,18,25], only two have reported SGE and DGE loci *acting on the same phenotype.* One of these reported that DGE loci explain a much greater proportion of phenotypic variance than SGE loci[17] while the other found similar effect sizes for individual SGE and DGE loci[8]. Given the sparsity of information, expectations on the effect sizes of SGE are difficult to build.

In order to improve our understanding of the architecture of SGE, we leveraged an existing dataset of 170 behavioural, physiological and morphological phenotypes measured in outbred “CFW” laboratory mice[26,27] (Figure 1c). We studied both SGE and DGE acting on each of these 170 phenotypes (Figure 1b) using polygenic models and GWAS. Specifically, we investigated whether SGE and DGE arise from similar loci, and compared the effect sizes of SGE loci to those of DGE loci.

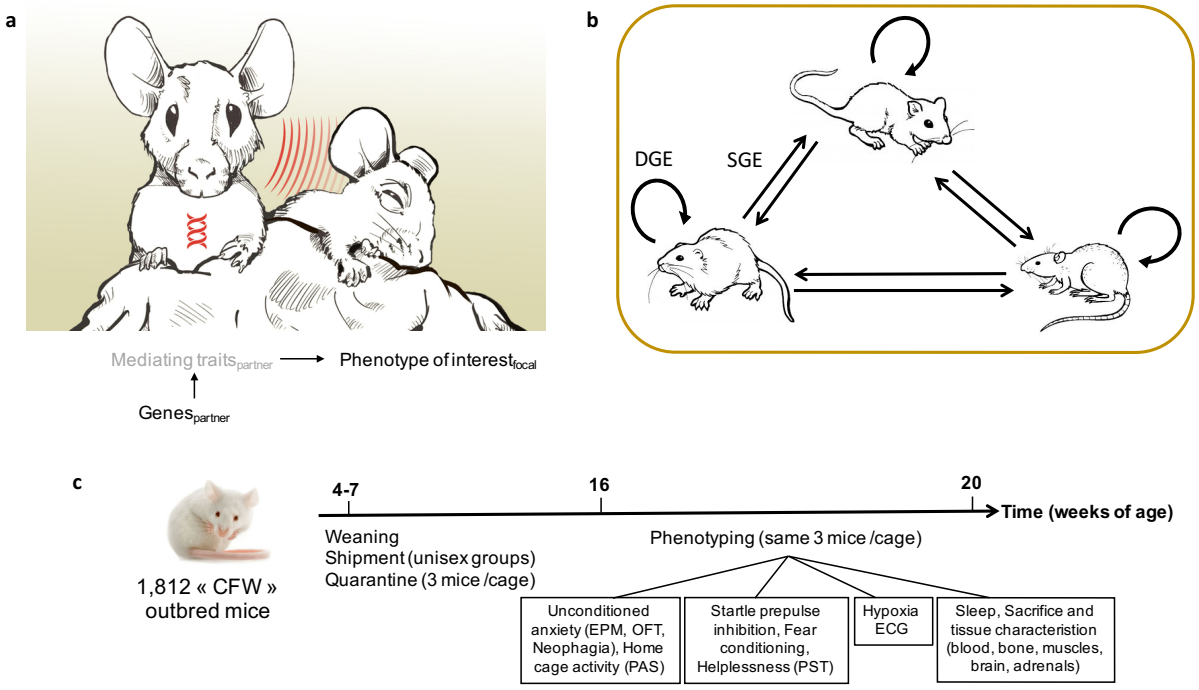

Figure 1 *Illustration of social genetic effects (SGE), definition of specific terms used throughout the manuscript, and experimental design. (a) SGE arise when two individuals interact and heritable traits of one influence the phenotype of the other. In other words, genotypes of the "social partner" influence - through "mediating traits" - the "phenotype of interest", measured in the "focal individual". Importantly, these mediating traits are not measured. (b) 1,812 "CFW" outbred mice were housed in groups of 3 mice per cage. SGE and DGE contributed by each mouse were modelled, such that each mouse served as both focal individual and cage mate in our analyses. (c) Housing conditions and phenotyping.*

Results

Genome-wide genotypes and 200 behavioural, physiological and morphological phenotypes for 2,073 commercially-available, outbred CFW mice were available from Nicod et al.[26] and Davies et al.[27]. Males were always housed with males and females with females, and mice were left undisturbed in their cages for at least nine weeks before phenotyping started (Figure 1c). We only kept mice that had the same two cage mates over the course of the experiment (1,869 total). Furthermore, we excluded 57 mice that formed genetic substructures (see Methods) so that the remaining 1,812 mice were as equally related as possible while retaining as large a sample size as

119 possible. We analysed a subset of 170 phenotypes that could be satisfactorily
120 normalised (see Methods). The exact number of mice used for each phenotype, is
121 shown in Supplementary Table 1.
122
123 **Aggregate contribution of SGE**
124 We first estimated the aggregate contribution of SGE to each phenotype (i.e. the sum
125 of SGE across the genome). To do so, we used the variance decomposition method
126 detailed in Baud et al.[9], which features random effects for DGE, SGE, direct and social
127 environmental effects, and "cage effects" (see Methods). SGE, in aggregate,
128 explained up to 22% (+/- 6%) of variation in serum LDL levels and an average of 11%
129 across 9 phenotypes with significant aggregate SGE (FDR < 10%, Supplementary
130 Table 1). Those 9 phenotypes included behavioural (helplessness, a murine model for
131 depression), physiological (serum LDL cholesterol, wound healing, blood eosinophils,
132 serum alpha-amylase concentration, blood platelets, acute hypoxic response), and
133 morphological (weight of adrenal glands) traits. For many of these phenotypes, the
134 pathways underlying social effects, i.e. the traits of cage mates that mediate social
135 effects, are unknown.
136
137 **Overlap between SGE and DGE loci acting on the same phenotype**
138 The polygenic model used for variance decomposition fits a correlation coefficient ρ
139 that measures the correlation between the SGE and DGE random effects of the model
140 (see Methods). Thus, ρ quantifies the extent to which SGE and DGE acting on the
141 same phenotype arise from similar loci, with similar effect sizes. We stress that, in this
142 section and throughout the manuscript, we compare SGE and DGE *acting on the*
143 *same phenotype* (but do this for all 170 phenotypes). Simulations showed that the
144 precision with which ρ can be estimated depends on the aggregate contribution of both
145 SGE and DGE (Supplementary Figure 1), so we limited the analysis of ρ to 28
146 phenotypes for which both aggregate SGE and aggregate DGE explained more than
147 5% of phenotypic variation. The value of ρ varied between -0.28 (+/-0.35) and 1(+/-
148 0.09) across these traits, with an average of 0.42 (Figure 2 and Supplementary Table
149 1). For 10 out of the 28 phenotypes where ρ could be more precisely estimated, ρ was
150 significantly different from zero (nominal $P < 0.05$), suggesting that loci affecting a
151 phenotype directly also sometimes influence the same phenotype of cage mates. The

strongest evidence for shared SGE and DGE loci ($\rho \neq 0$ at Bonferroni-corrected $P < 0.05$) was for healing from an ear punch, weight of the adrenal glands, serum LDL cholesterol levels, and mean platelet volume.

We also evaluated evidence that $|\rho|$ was different from one (i.e. ρ different from one and minus one) in order to empirically evaluate the widely-influential model of "phenotypic contagion". Phenotypic contagion or "spread" is a model for social effects whereby the phenotype of interest of a focal individual is affected by the same phenotype of their social partners. In humans, cognitive susceptibility to depression, alcohol consumption, stress, obesity and educational attainment, for example, have been shown to be "contagious" or "spread" across college roommates, spouses, friends, or parent/offspring[10-12,28-32]. As a result, phenotypic contagion has shaped the way we think about social effects: for example, phenotypes unlikely to spread have been used to cast doubt on social network effects[33]. Here we leveraged the parameter ρ to test whether phenotypic contagion was sufficient to account for SGE: under a model of pure phenotypic contagion, $|\rho|$ is expected to be equal to one; on the contrary, if traits of social partners other than the phenotype of interest mediate social effects, $|\rho|$ is expected to be different from one. We found that $|\rho|$ was significantly different from one (nominal $P < 0.05$) for 10 out of 28 phenotypes. The most significant P value (0.00066, significant after Bonferroni correction) was found for immobility in the first two minutes of the Porsolt swim test, a measure of helplessness that is relevant to depression. This latter result suggests that phenotypes that spread may additionally be affected by other traits of social partners. These results motivate the use of sgeGWAS as a tool to more broadly understand social effects.

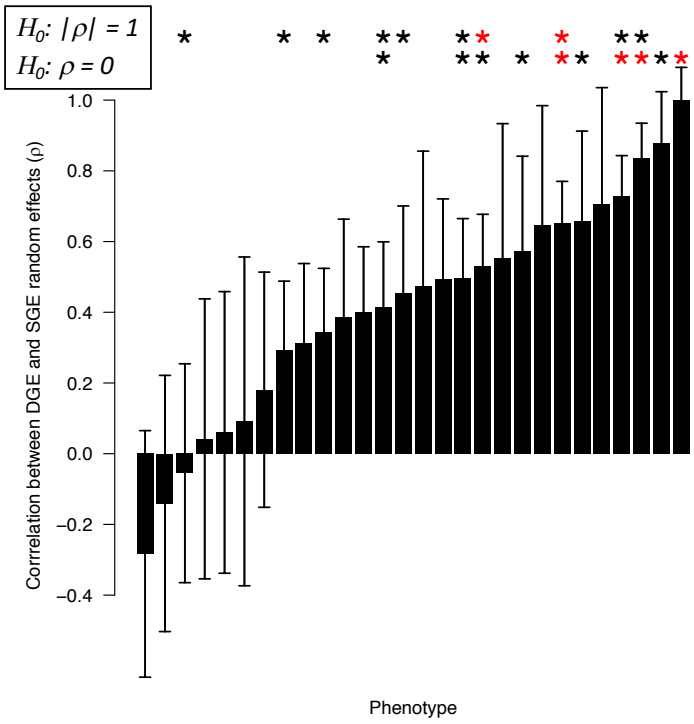

Figure 2 *Correlation ρ between SGE and DGE random effects (see Methods). The 28 phenotypes included in this table are those for which the correlation ρ could be more precisely estimated, i.e. phenotypes with aggregate SGE and aggregate DGE > 5%. The bars show the standard errors. The stars represent the P value for rejecting H_0: ρ = 0* (bottom) and *H_0: $|\rho|$ = 1 (i.e. pure phenotypic contagion, top). * denotes nominal P value < 0.05, * denotes Bonferroni-corrected P value < 0.05.*

sgeGWAS and dgeGWAS of 170 phenotypes

To map SGE and following Biscarini et al.[13] and Brinker et al.[25], we calculated the "social genotype" of a mouse at a variant as the sum of the reference allele dosages of its cage mates at the variant, and tested for association between social genotype and phenotype. In order to avoid spurious associations, we accounted for background SGE, DGE and non-genetic effects using an extension of the variance components model used for variance decomposition. In the sgeGWAS we also accounted for DGE of the variant tested for SGE, by including direct genotypes at the locus as a covariate (See Methods). Similarly, in the dgeGWAS we included social genotypes at the locus as a covariate. We hereafter refer to this strategy as "conditioning". We found that conditioning was necessary to avoid spurious associations in the sgeGWAS due to co-localised DGE. As we show in the Supplementary Note, this problem originates from the use of each mouse as both focal individual and cage mate in the analysis, a

strategy that has been used before to maximise sample size when all individuals are phenotyped and genotyped[13,25]. Importantly, spurious associations may arise even if all individuals are strictly unrelated (Supplementary Note). Using each mouse as both focal individual and cage mate in the analysis results in direct and social genotypes at a locus being correlated (Supplementary Figures 2a and 2b), which leads to sgeGWAS P values being inflated under the null in the presence of a simulated, co-localised large-effect DGE (Supplementary Figure 2c). This issue has not previously been reported and may have resulted in spurious SGE associations when conditioning was not used[13].

We show that conditioning on direct genotypes at the locus yielded calibrated sgeGWAS P values for null phenotypes (Supplementary Figure 2d), indicating that genome-wide significance thresholds may be derived for sgeGWAS by permuting social genotypes (see Methods), as long as conditioning is used in the analysis. A power analysis suggested that conditioning may slightly decrease power to detect SGE in the absence of co-localised DGE, particularly when direct and social genotypes are highly correlated (Supplementary Figure 3a and 3c) but would increase power if the locus also gave rise to DGE (Supplementary Figures 3b and 3d).

In order to compare, for each phenotype, the results of sgeGWAS and dgeGWAS, we defined loci based on the average size of the 95% confidence interval in this population, namely 1.5Mb[26], and, following Nicod et al.[26], used a per-phenotype FDR approach (see Methods). At a 10% FDR threshold, sgeGWAS identified 24 genome-wide significant loci for 17 of the 170 phenotypes (Figure 3 and Supplementary Table 2). In comparison, dgeGWAS identified 121 genome-wide significant loci for 63 phenotypes at the same threshold (Figure 3 and Supplementary Table 3).

There was no overlap between genome-wide significant SGE and DGE loci *acting on the same phenotype*. However, variants at genome-wide significant SGE loci were enriched in small P values in the corresponding dgeGWAS (Supplementary Figure 4). Together these results suggest a partially distinct basis for SGE and DGE *acting on the same phenotype* (i.e. partially different loci and/or effect sizes), which is consistent with the results from the analysis of the correlation parameter ρ.

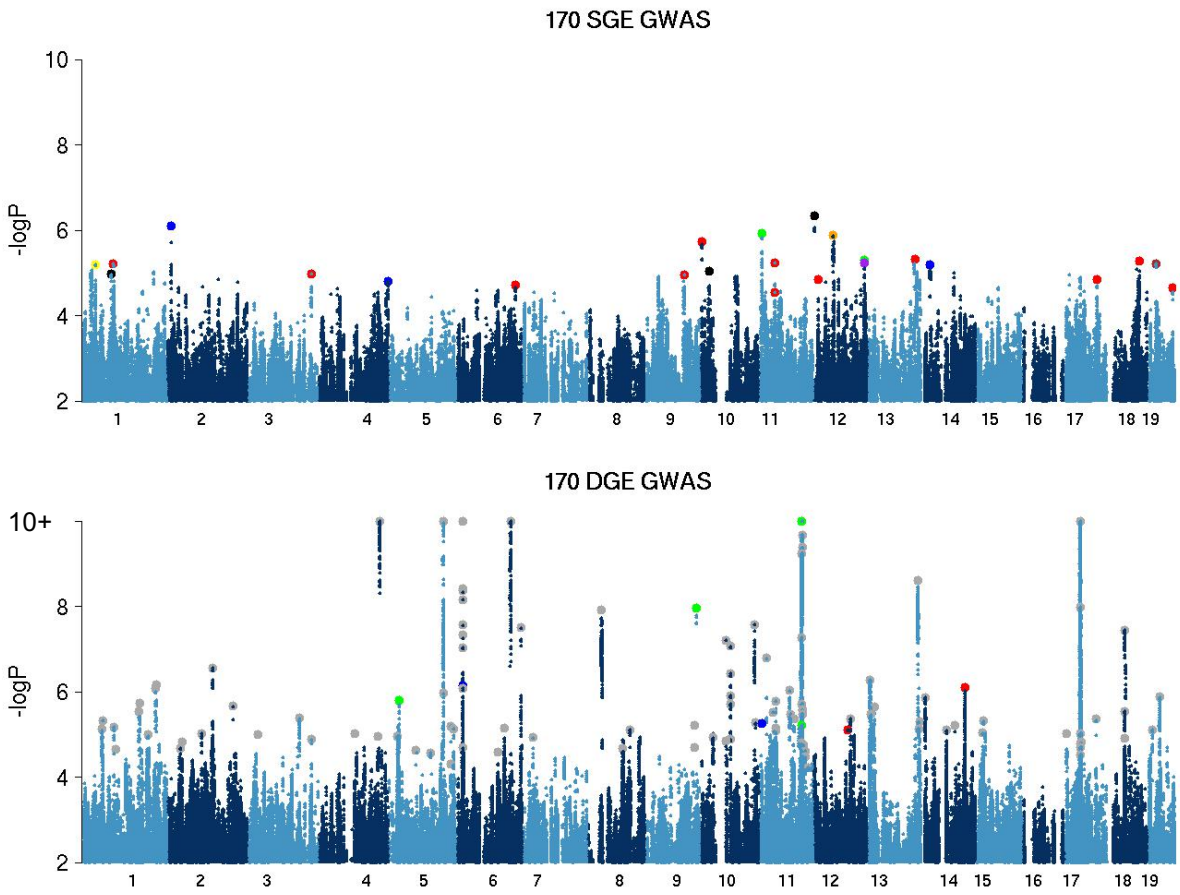

Figure 3 *Superimposed manhattan plots corresponding to 170 sgeGWAS (top panel) and 170 dgeGWAS (bottom panel) of the same phenotypes. DGE associations with a –logP greater than 10 were plotted at –logP 10 (as indicated by 10+). Data points with negative log P < 2 are not shown. Lead variants for all genome-wide significant SGE and DGE loci are represented with a larger dot. In the SGE panel, each color corresponds to a class of phenotypes: behavioural (red, includes 7 behavioural phenotypes with a detected SGE locus), adult neurogenesis (black, 2 phenotypes), immune (orange, 1 phenotype), haematological (yellow, 1 phenotype), blood biochemistry (blue, 2 phenotypes), bone phenotypes (green, 2 phenotypes), heart function (brown, 1 phenotype), and lung function (purple, 1 phenotype). In the DGE panel, a genome-wide significant locus is colored grey when the corresponding phenotype does not have a genome-wide significant SGE association; when the corresponding phenotype does have an SGE association, the same color is used as in the SGE panel.*

Compared to many other mouse populations used for mapping, linkage disequilibrium decays rapidly in the CFW population[26,34]. At each genome-wide

significant SGE locus we identified candidate genes, prioritising well-annotated genes (see Methods). At five genome-wide significant SGE loci we identified a single candidate gene (Supplementary Table 2, locus zoom plots in Supplementary Figure 5): *Abca12*, a gene known for its involvement in lipid transport and homeostasis in the skin[35], at an SGE locus for adult neurogenesis in the hippocampus; *Epha4*, a signalling genes involved in neural system function, at an SGE locus for helplessness; *H60c*, a poorly characterised gene potentially involved in skin immunity[36], at an SGE locus for locomotor activity; *Pgk1-rs7*, a pseudogene of phosphoglycerate kinase-1, at and SGE locus for sleep; and *Ighv5-9-1*, a variable region of the T cell receptor, at an SGE locus for response to hypoxia. None of these genes have known direct effects that can easily explain the observed SGE, nor did they seem to have DGE on the phenotype in this dataset (Supplementary Figure 5), so the results of our sgeGWAS point to yet unknown traits of cage mates that influence the five phenotypes above.

Of these candidate genes, one, *Epha4*, has previously been associated with the phenotype of interest. *Epha4* expression in the hippocampus was found to be affected by chronic mild stress in mice and responsive to antidepressant treatment[37]. We also found suggestive DGE of *Epha4* on helplessness (Supplementary Figure 5), confirming that some level of phenotypic contagion was likely for that phenotype. The other candidate genes did not immediately permit to generate hypotheses on the traits of cage mates mediating the social effects. To gain such insights from the results of sgeGWAS, it is likely that other data types (e.g. gene expression) will need to be integrated. Alternatively, larger sample sizes would permit identification of additional SGE loci, some of which might immediately provide insights into the traits of partners that mediate social effects. SgeGWAS, in that respect, is similar to dgeGWAS[14,38,39].

Architecture of SGE and comparison with that of DGE

Despite being carried out on the same individuals and phenotypes, and in a perfectly analogous manner, sgeGWAS identified fewer genome-wide significant associations than dgeGWAS (24 associations for 17 phenotypes and 121 associations for 63 phenotypes respectively). As the determinants of power for SGE have not been investigated, it is not clear whether we had more or less power to detect SGE associations compared to DGE associations. In order to get a better understanding of this issue, we simulated local SGE or DGE arising from a single causal variant and calculated power to detect these associations. Briefly (see Methods), we considered

random groups of two or three mice per cage, and simulated phenotypes arising from the sum of local genetic effects (DGE or SGE), polygenic effects (DGE and SGE), and non-genetic effects. We simulated local SGE according to two alternative generative models, both consistent with the analysis model used for sgeGWAS: an "additive" model according to which social effects add up across cage mates, and a "proportional" model corresponding to a scenario where the focal mouse interacts with only one cage mate at a time, spending equal time with each cage mate. Note that the additive and proportional models are equivalent when there is a single cage mate (i.e. two mice per cage). For all three types of local effects (DGE, additive SGE and proportional SGE) we simulated the same allelic effect. Finally, we considered variants with low, medium or high minor (direct) minor allele frequencies (MAF, see Methods).

Our simulations showed that power always increased with MAF (Figure 3a). At a given MAF, simulating SGE from a single cage mate led to the same power for SGE and DGE. Simulating SGE arising from two cage mates additively led to greater power to detect SGE associations compared to DGE associations. In contrast, simulating SGE arising from two cage mates under the proportional model led to lower power for SGE compared to DGE. These results are consistent with the fact that, for a given sample size, power to detect a local effect (DGE or SGE) is determined by the sample variance of the simulated effect. Noting MAF as p, number of cage mates as N, and allelic effect as b, that variance is expected to be $2p(1-p)b^2$ for DGE, $2Np(1-p)\ b^2$ for SGE simulated under the additive model, and $2Np(1-p)/N^2\ b^2$ for SGE simulated under the proportional model (see Methods). In conclusion, our simulations showed that power to detect individual SGE associations is determined not only by allelic effect and MAF of the causal variants, but also by the way SGE arise across cage mates (additively or not) and the number of cage mates. In the real data, the way SGE arose across cage mates is not known, so it is not possible to determine the primary cause for the smaller number of genome-wide significant SGE associations compared to DGE associations.

Comparing genome-wide significant SGE and DGE associations in terms of proportion of phenotypic variance explained yielded two main results: firstly, individual genome-wide significant SGE associations explained a maximum of 2.5% of phenotypic variance, while eleven genome-wide significant DGE associations explained more than 5% of phenotypic variance and up to 40% (Figure 3b, Supplementary Table 2 and Supplementary Table 3). Average values were 1.8% for

SGE and 2.7% for DGE associations. As these results are born from the analysis of 170 phenotypes, it suggests that SGE associations will generally be more difficult to detect than DGE associations. Secondly, for each phenotype we compared the variance explained jointly by all genome-wide SGE (respectively DGE) associations to the variance explained by SGE (respectively DGE) in aggregate. We found that genome-wide significant associations explained a large proportion of the corresponding genetic variance for both SGE and DGE (Figure 3c). More precisely, across 5 phenotypes with aggregate contribution of SGE greater than 5% and at least one genome-wide significant SGE association, we found that an average of 32.5% of the aggregate variance was explained by genome-wide significant associations. For DGE, that figure was calculated across 55 phenotypes and was equal to 32.1%. The proportion of aggregate variance explained by genome-wide significant associations may seem large given the relatively small number of genome-wide significant associations per phenotype (e.g. compared to humans[40]), but is consistent with studies of DGE in other outbred laboratory rodent populations[41,42] and are the result of a relatively small number of variants segregating in the CFW population with relatively high MAFs[26]. In conclusion, our results are consistent with oligo- or polygenic architectures for SGE. A more precise estimation of the number of loci involved will only be possible when more SGE associations are discovered in other datasets.

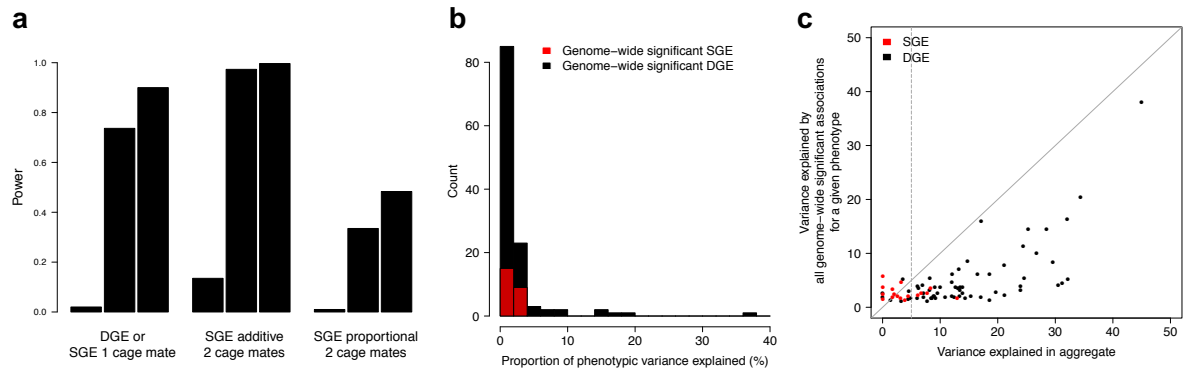

Figure 3 *Power to detect local SGE and DGE, and characterisation of the architecture of SGE and DGE. (a) Power to local genetic effects in simulations. Three types of local genetic effects were simulated: DGE (or, equivalently, SGE arising from a single cage mate), SGE arising from two cage mates under an additive model, and SGE arising from two cage mates under a proportional model (see Main Text). For each type of effect, results are shown (left to right) for variants with low MAF (MAF < 0.05), medium MAF (0.225<MAF<0.275) and high MAF (MAF>0.45) (MAF: minor allele frequency,*

defined based on direct genotypes). (b) Histogram of the proportion of phenotypic variance explained by individual genome-wide significant SGE (red) and DGE (black) associations. (c) Comparison, for each phenotype, of the variance explained by social (red) and direct (black) genetic effects in aggregate (x axis) and the total variance explained jointly by all genome-wide significant SGE or DGE associations for a phenotype (y axis). Each dot corresponds to a phenotype with at least one genome-wide significant association.

Discussion

In this study we performed the comparative analysis of both SGE and DGE acting on each one of 170 behavioural, physiological and morphological phenotypes measured in outbred laboratory mice, using polygenic models and GWAS. Our results provided two key insights into the architecture of these complex traits: first, SGE and DGE *acting on the same phenotype* typically arise from partially different loci and/or loci with different effect sizes; secondly, SGE associations tend to explain less phenotypic variation than DGE associations. As we analysed a broad range of phenotypes, the insights we gained are likely to generalize to other populations and phenotypes.

For 10 phenotypes we uncovered evidence that SGE and DGE were significantly correlated. For example, ρ was significantly different from zero for the two measures of helplessness included in this dataset. This result is consistent with prior evidence that mood spreads across social partners[28,43]. It is also consistent with the observation that, in this study, two out of the three genome-wide significant SGE loci for helplessness have suggestive direct effects on helplessness - direct effect that are further supported by prior reports that *Epha4*, the candidate gene at one of the loci, is associated with depression and responds to antidepressant treatment[37]. The pathways that mediate non-zero correlations between SGE and DGE for other phenotypes were not always obvious (e.g. healing from an ear punch, serum LDL cholesterol levels) but warrant further investigation of SGE and DGE.

A key result from our study is empirical evidence that phenotypic contagion is often not sufficient to account for social effects, even when it does play a role. Indeed, for 10 out of 28 tested phenotypes we found that $|\rho|$ was significantly different from one, including the two aforementioned measures of helplessness. This result supports

efforts to discover other traits of social partners that mediate social effects, and points to sgeGWAS as a way to do so. It is important to bear in mind, however, that SGE only capture the genetic component of the traits of partners that mediate social effects. Hence, traits that are mostly non-genetically determined will be missed by SGE studies.

Our results on the variance explained by individual SGE loci are an important contribution towards understanding the architecture of SGE and will help design future experiments such as sgeGWAS. In particular, the fact that SGE loci never explained a large fraction of phenotypic variance (max 2.5%), while in comparison 11 DGE loci explained more than 5% of phenotypic variation, shows that sgeGWAS will require larger sample sizes than dgeGWAS to be equally powered.

Finally, our study made several important methodological contributions that will help design, perform and interpret sgeGWAS, particularly in outbred populations where both DGE and SGE contribute to phenotypic variation. Specifically, our study improved our understanding of the determinants of power for SGE and we showed that correlations between direct and social genotypes at a locus need to be accounted for to avoid spurious associations. These correlations arise when the same individuals serve as both focal individuals and social partners in the analysis, even if all individuals are unrelated. Importantly, similar correlations between direct and social genotypes, but potentially much stronger, may arise for different reasons in other datasets, notably when focal individuals and social partners are related, or as a result of direct assortments (e.g. assortative mating[44,45], homophily between friends[10]). The methods we presented here will help avoid spurious associations in such situations. Importantly, we contribute software and code to reproduce our analyses or analyse other datasets.

Methods

Phenotypes and experimental variables

Phenotypes and experimental variables (covariates) for 1,934 Crl:CFW(SW)-US_P08 (CFW) mice were retrieved from http://wp.cs.ucl.ac.uk/outbredmice/. We normalized

each phenotype using the boxcox function (MASS package[46]) in R, and excluded phenotypes that could not be normalised satisfactorily (lambda outside of -2 to 2 interval). The subset of covariates used for each phenotype is indicated in Supplementary Table 1. Because data for some phenotypes were missing for some mice, the sample size varied. The sample size for each phenotype after all filtering (see below) is indicated in Supplementary Table 1.

Caging information

Mice were four to seven weeks old when they arrived at the phenotyping facility. They were grouped with their cage mates and then spent nine to twelve weeks undisturbed in quarantine. They spent a further four weeks together during phenotyping. Males were always housed with males and females with females.

Cage assignments were not included in the publicly available dataset but were provided by the authors upon request and are now provided in Supplementary Table 4. Cage assignments were recorded at eleven time points throughout the study and showed that a few mice were taken out of their original cages and singly housed, presumably because they were too aggressive to their cage mates. When this happened, we excluded all the mice in that cage from the analysis. We also excluded cages where some of the mice were "genetically close" (as defined below) to many other mice. Finally, we only retained cages with exactly three mice per cage. Although from the sleep test on all mice were singly housed, we still investigated "persistent" SGE on sleep and tissue phenotypes (persistence over one day for sleep phenotypes and over a few days for tissue measures).

Genome-wide genotypes

From http://wp.cs.ucl.ac.uk/outbredmice/ we retrieved both allele dosages for 7 million variants and allele dosages for a subset of 353,697 high quality, LD-pruned variants (as described in Nicod et al.[26]). We used high quality, LD-pruned variants for all analyses but the identification of candidate genes at SGE loci (see below), for which we used the full set of variants.

Genetic relatedness matrix (GRM) and exclusion of "genetically close" mice

The genetic relatedness matrix was calculated as the cross-product of the dosage matrix after standardizing the dosages for each variant to mean 0 and variance 1.

We excluded whole cages of mice based on GRM values as follows: we defined a "close pair" of mice as having a GRM value greater than 0.3 (based on the histogram of all GRM values). 199 mice in 145 cages were involved in such close pairs. Excluding all 145 cages would have resulted in excluding 435 mice out of a total of 1,812, which would have led to substantially reduced power for sgeGWAS and dgeGWAS. Thus, we made a compromise and only excluded the 19 cages that were involved in 4 or more close pairs (57 mice excluded).

Variance decomposition

The same method as described in details in Baud et al.[9] was used. Briefly, the model used was:

$$y_f = X_f \underline{b} + a_{D,f} + e_{D,f} + Z_f \underline{a_S} + Z_f \underline{e_S} + W_f \underline{c} \qquad (0)$$

y_f is the phenotypic value of the focal mouse f, X_f is a row of the matrix X of covariate values and b a column vector of corresponding estimated coefficients. $\underline{a_{D,f}}$ is the additive direct genetic effects (DGE) of f. Z_f is a row of the matrix Z that indicates cage mates (importantly $Z_{i,i} = 0$) and $\underline{a_S}$ the column vector of additive social genetic effects (SGE). $\underline{e_D}$ refers to direct environmental effects and $\underline{e_S}$ to social environmental effects. W_f is a row of the matrix W that indicates cage assignment and c the column vector of cage effects.

The joint distribution of all random effects is defined as:

$$\begin{bmatrix} \underline{a_D} \\ \underline{a_S} \\ \underline{e_D} \\ \underline{e_S} \\ \underline{c} \end{bmatrix} \sim \mathrm{MVN}\left(0, \begin{bmatrix} \sigma^2_{A_D}\mathrm{A} & \sigma_{A_{DS}}\mathrm{A} & 0 & 0 & 0 \\ \sigma_{A_{DS}}\mathrm{A}^T & \sigma^2_{A_S}\mathrm{A} & 0 & 0 & 0 \\ 0 & 0 & \sigma^2_{E_D}\mathrm{I} & \sigma_{E_{DS}}\mathrm{I} & 0 \\ 0 & 0 & \sigma_{E_{DS}}\mathrm{I}^T & \sigma^2_{E_S}\mathrm{I} & 0 \\ 0 & 0 & 0 & 0 & \sigma^2_C\mathrm{I} \end{bmatrix}\right)$$

where A is the GRM and I the identity matrix.

The phenotypic covariance is:

$$C_{i,j} = cov\,(y_i\,, y_j)$$

$$= \sigma^2_{A_D}\,A_{i,j} + \sigma_{A_{DS}} + \sigma^2_{A_S}(ZAZ^T)_{i,j} + \sigma^2_{E_D}\,I_{i,j} + \sigma_{E_{DS}}\{\,(IZ^T)_{i,j}$$

$$+ (ZI^T)_{i,j}\,\} + \sigma^2_{E_S}(ZIZ^T)_{i,j} + \sigma^2_C\,(WIW^T)_{i,j}$$

The variances explained by DGE and SGE were calculated respectively as $sampleVar\left(\sigma^2_{A_D}\,A\right)$ / $sampleVar(C)$ and $sampleVar\left(\sigma^2_{A_S}(ZAZ^T)\right)$ / $sampleVar(C)$ where $sampleVar$ is the sample variance of the corresponding covariance matrix: suppose that we have a vector $\underline{x}$ of random variables with covariance matrix M, the sample variance of M is calculated as

$$sampleVar(M) = \frac{Tr(PMP)}{n-1}$$

Tr denotes the trace, n is the sample size, and $P = I - \frac{11'}{n}$ [47,48].

For those phenotypes where body weight was included as a covariate, we checked that this did not lead to systematically increased (or decreased) estimates of the aggregate contribution of SGE (collider bias).

Significance of variance components was assessed using a two-degree of freedom log likelihood ratio (LLR) test (i.e., the test statistics was assumed to follow a two-degree of freedom chi2 distribution under the null). Note that this testing procedure is conservative.

The Q value for the aggregate contribution of SGE was calculated for each phenotype using the R package qvalue[49]. Significant contributions at FDR < 10% were those with Q value < 0.1.

Correlation between DGE and SGE

The correlation ρ between $\underline{a_D}$ and $\underline{a_S}$ was calculated as:

$$\rho = \frac{\sigma_{A_{DS}}}{\sigma_{A_D} \times \sigma_{A_S}}$$

ρ reflects the correlation between SGE and DGE *acting on the same phenotype,* similarly to how "traditional" genetic correlations measure the correlation between DGE on two traits; ρ can actually be interpreted as the correlation between DGE on

the traits of cage mates mediating social effects and DGE on the phenotype of interest itself.

We tested whether ρ was significantly different from 0 and whether $|\rho|$ was significantly different from 1 using a one-degree of freedom LLR test.

Simulations 1: for Supplementary_Figure1.

Phenotypes were simulated based on the genotypes and cage relationships of the full set of 1,812 mice. Phenotypes were drawn from model (0) with the following variances: $\sigma^2_{A_D} = 15$, $\sigma^2_{A_S} = 8$, $\rho_{A_{DS}} = 0.47$, $\sigma^2_{E_D} = 22$, $\sigma^2_{E_S} = 16$, $\rho_{E_{DS}} = -0.97$, $\sigma^2_C = 26$. These variances correspond to the median value of estimates across traits with aggregate SGE and DGE > 5%. After building the phenotypic covariance matrix, the sample variance of the simulations was calculated and used to calculate "realised" simulation parameters from the "target" parameters above. The realised parameters were used for comparison with the parameters estimated from the simulations.

Definition of "social genotype" for sgeGWAS

In the sgeGWAS, we assumed additive effects across cage mates and calculated the "social genotype" of a mouse as the sum of the reference allele dosages of its cage mates. The same assumptions were made by Biscarini *et al.*[13] and Brinker *et al.*[25].

Correlation between direct and social genotypes at a variant

Spearman's rank correlation coefficient was used. We tested whether the correlation was different from 0 using the function cor.test in the R package stats[50].

Models used for sgeGWAS and dgeGWAS

To test SGE of a particular variant, we compared the following two models:

$$y_f = X_f\underline{b} + a_{D,f} + e_{D,f} + Z_f\underline{a_S} + Z_f\underline{e_S} + W_f\underline{c} + G_f b_D \qquad \text{(1, null)}$$

$$y_f = X_f\underline{b} + a_{D,f} + e_{D,f} + Z_f\underline{a_S} + Z_f\underline{e_S} + W_f\underline{c} + G_f b_D + Z_f G b_S \quad \text{(2, alternative)}$$

Here, G is the vector of direct genotypes at the tested variant, b_D the estimated coefficient for local DGE and b_S the estimated coefficient for local SGE.

The models were fitted using LIMIX[51,52] with the covariance of the model estimated only once per phenotype, in the model with no local genetic effect (model 0).

The significance of local SGE was calculated by comparing models (1) and (2) with a 1-degree of freedom LLR test.

We refer to the inclusion of $G_f b_D$ in model (1, null) as "conditioning".

dgeGWAS was carried out similarly, by comparing the null model (3) below and model (2) above:

$$y_f = X_f\underline{b} + a_{D,f} + e_{D,f} + Z_f\underline{a_S} + Z_f\underline{e_S} + W_f\underline{c} + Z_f G b_S \quad \text{(3, null)}$$

We refer to the inclusion of $Z_f G b_S$ in model (3, null) as "conditioning".

Identification of genome-wide significant associations

Because we wanted to compare the architecture of DGE and SGE *for each phenotype independently*, we adopted the per-phenotype FDR approach used by Nicod et al.[26]. Had we used a study-wide FDR approach instead, the comparison of SGE and DGE loci for a given phenotype would have depended on the SGE and DGE loci identified for the other phenotypes in the dataset.

The procedure we used to control the FDR accounts for the fact that we report loci rather than individual variants[53], where a locus is defined as the 1.5 Mb-wide window around a SNP (this window size is the average 95% confidence interval for DGE QTLs in [26]). More precisely, for each phenotype and for each type of genetic effect (social and direct), we ran 100 "permuted GWAS" by permuting the rows of the matrix of social (respectively direct) genotypes, and testing each variant at a time using the permuted genotypes together with the un-permuted phenotypes, covariates, GRM and matrix of direct (respectively social) genotypes (for conditioning). See [52,54] for references on this permutation approach. For each permutation we then compiled a list of loci that would be significant at a nominal P value of 0.01. Using the un-permuted data, we similarly compiled a list of loci that would be significantly associated at a nominal P value of 0.01. Ordering the latter in order of decreasing significance and

going down the list, we calculated for each locus an associated FDR until the FDR was above 10%. For a given P value x, the FDR was calculated as:

$$FDR(x) = \frac{\#\ loci\ with\ P < x\ in\ permuted\ data}{100 \times \#\ loci\ with\ P < x\ in\ unpermuted\ data}$$

We report only those loci whose P value corresponds to an FDR < 10%.

Definition of candidate genes at associated loci (Table 2)

At each significantly associated locus we defined a 1.5Mb window centred on the lead variant, identified all the variants that segregate in this window based on the full set of 7M variants, and reran the sgeGWAS locally with all the variants at the locus. We highlighted those genes that are located within the most significantly associated segments and whose MGI symbol does not start by 'Gm', 'Rik', 'Mir', 'Fam', or 'Tmem' in order to enrich the reported sets in genes with known function.

Variance explained by a genome-wide significant association

The variance explained by a genome-wide significant SGE association was estimated in an extension of model (0) with additional fixed effects for both direct and social effects of lead SNPs at all genome-wide significant SGE loci (the lead SNP being the SNP with the most significant P value at the locus in the sgeGWAS). After fitting the model, the variance was calculated as:

$$\frac{var(ZGb_S)}{\sum var(X_c b_c) + \sum var(Gb_D) + \sum var(ZGb_S) + sampleVar(C)}$$

where $sampleVar(C)$ is the sample variance of the covariance matrix in this model.

The variance explained by a genome-wide significant DGE association was estimated in a similar model but considering all genome-wide significant DGE associations and calculated as:

$$\frac{var(Gb_D)}{\sum var(X_c b_c) + \sum var(Gb_D) + \sum var(ZGb_S) + sampleVar(C)}$$

598

599 *Variance explained jointly by all genome-wide significant SGE or DGE associations*
600 *for a phenotype*

601

602 The variance explained jointly by all significant SGE associations was estimated using
603 the same model as above with all genome-wide significant SGE associations and
604 calculated as:

606 $$\frac{\sum var(ZGb_S)}{\sum var(X_c b_c) + \sum var(Gb_D) + \sum var(ZGb_S) + sampleVar(C)}$$

605

607 The variance explained jointly by all significant DGE associations was estimated using
608 the same model as above with all genome-wide significant DGE associations and
609 calculated as:

610

612 $$\frac{\sum var(Gb_D)}{\sum var(X_c b_c) + \sum var(Gb_D) + \sum var(ZGb_S) + sampleVar(C)}$$

611

613 *Simulations 2: for Supplementary Figure 2d.*

614

615 Phenotypes were simulated based on the genotypes and cage relationships of the full
616 set of 1,812 mice. Phenotypes were simulated as the sum of random effects and local
617 DGE (from model (1)), with the following parameters: $\sigma^2_{A_D} = 5$ or 20, $\sigma^2_{A_S}$ = 5 or 20,
618 $\rho_{A_{DS}}$= 0.5, $\sigma^2_{E_D}$= 30, $\sigma^2_{E_S}$= 30, $\rho_{E_{DS}}$ = -0.97, σ^2_C = 25. The values for $\rho_{A_{DS}}$, $\sigma^2_{E_D}$, $\sigma^2_{E_S}$, $\rho_{E_{DS}}$,
619 and σ^2_C were close to the median of the corresponding estimates from the real data.
620 $\sigma^2_{A_D} = 5$ and $\sigma^2_{A_S} = 5$ correspond to low polygenic effects in the real data, and $\sigma^2_{A_D} =$
621 20 and $\sigma^2_{A_S} = 20$ correspond to high polygenic effects in the real data. We simulated
622 local DGE at random variants in the genome, and simulated variances of 0, 5, 20 or
623 50.

624 The results we show in Supplementary Figure 2d are based on a subset of
625 simulations: $\sigma^2_{A_D} = 20$ and $\sigma^2_{A_S} = 20$ and local DGE variance of 20.

626

627 *Simulations 3: for* Supplementary Figure 3a-d, and Figure 3a.

628

Phenotypes were simulated based on the real genotypes but random cages for a random subset of 1,800 mice (in order to be able to draw full cages of 2 or 3 mice). Phenotypes were simulated as the sum of random effects, local DGE and local SGE (model (2) except for Z) with the following parameters: $\sigma^2_{A_D} = 17$, $\sigma^2_{A_S} = 17$, $\rho_{A_{DS}} = 0.65$, $\sigma^2_{E_D} = 19$, $\sigma^2_{E_S} = 15$, $\rho_{E_{DS}} = -0.8$, $\sigma^2_C = 25$. Those values correspond to the median estimates for phenotypes with aggregate SGE and DGE > 0.1.

We simulated local SGE and DGE at variants where direct and social genotypes were either lowly correlated (Spearman correlation negative log P value < 0.05) or more highly correlated (Spearman correlation negative log P value > 0.2), and had with low MAF (MAF < 0.05), medium MAF (0.225<MAF<0.275) or high MAF (MAF>0.45). We simulated local DGE with an allelic effect of 0 or 1 (1 corresponds to a large effect in the real data). We simulated local SGE under two alternative generative models: an "additive" model by using Z as in model (2) (i.e. filled with 0s and 1s) or a "proportional" model by using $Z' = {}^{Z}/_{N}$. In all cases we simulated an allelic effect of 0.2 (similar to the average allelic effect estimated in the SGE GWAS). The sample variance of the simulated local DGE term is $var(Gb_D) = 2p(1-p)\, b_D^2$; it is $var(ZGb_S) = 2\mathrm{N}p(1-p)\, b_S^2$ for the local SGE term simulated under the additive model, and $var\left(\frac{Z}{N}Gb_S\right) = 2\mathrm{N}p(1-p)/N^2\, b_S^2$ for the local SGE component simulated under the proportional model.

The results we show in Supplementary Figure 3a-d are based on a subset of simulations with group size 3 and are averaged across low, medium and high MAF. Power was calculated at a genome-wide significance threshold of negative log P 5, which is similar to the significance of associations detected at FDR < 10%.

The results we show in Figure 3a are based on a subset of simulations with group size 2 and 3, no local DGE, and averaged across high and low genotypic correlations. Power was also calculated at a genome-wide significance threshold of negative log P 5.

Scripts used in this study

All the scripts used in this study are available from http://github.com/limix/SGE. LIMIX can be downloaded from http://github.com/limix/limix.

662

663 # Acknowledgements

664

665 We would like to thank Na Cai and Robert W. Davis for helpful discussion of the data
666 from Nicod et al.[26] and Davies et al.[27], as well as Ewan Birney, Emma Huang, Richard
667 Mott, Abraham A. Palmer, and Sandra Sanchez-Roige for comments on a previous
668 version of this manuscript. AB was supported by a fellowship from the Wellcome Trust
669 (105941/Z/14/Z).

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