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

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Abstract

Genetics can be defined as the study of how an individual's genotype influences their phenotype ("direct genetic effects", DGE). However, an even broader view can also account for the influence of the genotype of environmental factors such as family members and other social partners ("social genetic effects", SGE). SGE in aggregate across the genome contribute to variation in many phenotypes, in many species(1-6). The goal of this study was to better understand how SGE arise from individual genetic loci. We focused on SGE arising between outbred laboratory mice sharing a cage and carried out the genome-wide association study of SGE and DGE for 170 phenotypes collected in 1,812 mice. We identified 24 and 120 genome-wide significant loci for SGE and DGE respectively (FDR < 10%). We found no overlap between genome-wide significant SGE and DGE loci acting on the same phenotype, which is consistent with our estimation of moderate correlations between SGE and DGE genome-wide. While eleven genome-wide significant DGE associations explained more than 5% of phenotypic variance, SGE associations explained no more than 2.5%. At five SGE loci we identified a single candidate gene and showed how individual SGE loci may help

identify traits of social partners that mediate social effects. Our results demonstrate that sgeGWAS has the potential to identify novel genetic loci contributing to inter-individual differences. They also illustrate how SGE loci may yield insights into the mechanisms of social influence. Finally, our comparative description of the architectures of SGE and DGE, together with the methods we have developed, will help design and analyse future sgeGWAS.

Main text

Introduction

Social interactions between two individuals can result in the phenotype of one individual being affected by genotypes of the other. Such effects arise when the phenotype of a focal individual is influenced by heritable traits of their social partner (Figure 1a) and are called social genetic effects (SGE) or indirect genetic effects(7-10).

SGE have been shown to contribute significantly and substantially to phenotypic variation in livestock, wild animals, plants and laboratory model organisms(1). In laboratory mice, SGE have been found to affect behavioural, physiological, and morphological traits, including phenotypes not *a priori* expected to be socially affected such as wound healing(2-5). In humans, effects of non-transmitted parental alleles have been detected on offspring's educational attainment(6, 11, 12). Thus, SGE are an important component of the genotype to phenotype path.

In addition, SGE may be used as a tool to investigate social effects, in particular identify traits of social partners affecting a phenotype of interest, measured in focal individuals. Indeed, identifying individual variants of social partners associated with the phenotype of interest, through genome-wide association study of SGE (sgeGWAS), could provide new insights into the pathways of social effects in a similar manner as GWAS of "traditional" direct genetic effects (DGE, effects of an individual's genotypes on its own phenotype) has provided insights into the "within-body" pathways of phenotypic variation(13). However, robust methods to perform sgeGWAS

are not established and such experiments will require information on the architecture of SGE(14).

The architecture of SGE is largely unknown, 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(3, 4, 15-18). Furthermore, it is currently unknown to what extent SGE loci overlap with DGE loci and how much phenotypic variance individual SGE loci explain. To address these questions and identify loci underlying SGE, we leveraged an existing dataset of 170 behavioural, physiological and morphological phenotypes measured in outbred "CFW" laboratory mice(19, 20) and studied both SGE arising from interactions between mice sharing a cage and DGE acting on each phenotype (Figure 1b and 1c). Our results and the methods we detail and validate will inform the design and analysis of future sgeGWAS carried out in outbred populations with any levels of relatedness and group sizes.

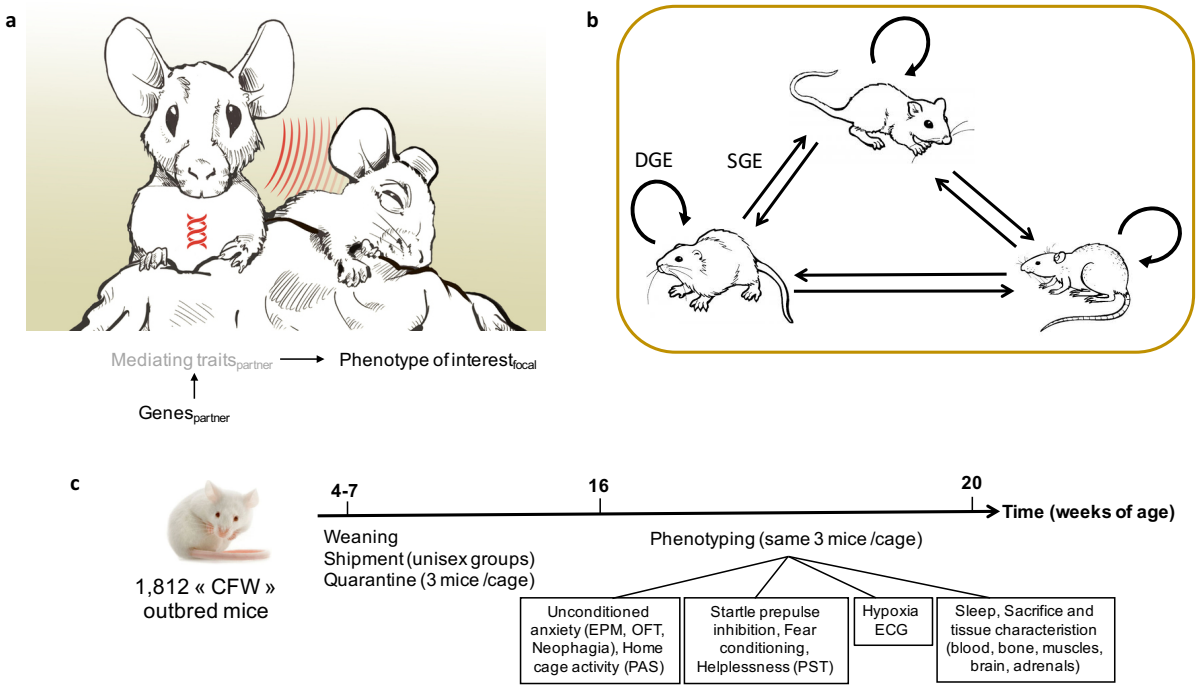


Figure 1 *Illustration of social genetic effects (SGE), definition of specific terms used throughout the manuscript, and experimental design. (a) SGE arise when two individuals interact and heritable traits of one influence the phenotype of the other. In other words, genotypes of the "social partner" influence - through "mediating traits" - the "phenotype of interest", measured in the "focal individual". Importantly, these*

mediating traits do not need to be measured or known. (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) Experimental design. The experimental paradigms used to collect the 170 phenotypes are listed.

Results

Genome-wide genotypes (both LD-pruned and non pruned, see Methods) and phenotypes for 2,073 CFW mice were available from Nicod et al.(19) and Davies et al.(20). Males were always housed with males and females with females, and mice interacted in their cages for a period of at least nine weeks before phenotyping (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 so that the remaining 1,812 mice were as equally related as possible while retaining as large a sample size as possible (see Methods).

Aggregate contribution of SGE

Initially we estimated the aggregate contribution of SGE (i.e. the sum of SGE across the genome) to all 170 phenotypes in the dataset, which include phenotypes that have never before been considered in a study of SGE (muscles and bones characteristics, response to hypoxia, electrocardiogram, and sleep). We used a random effect model for SGE and DGE as in Baud et al.(5) and found that SGE, in aggregate, explained up to 22% (+/- 6%) of variation in serum LDL levels and an average of 11% across 9 phenotypes with significant aggregate SGE (FDR < 10%, Supplementary Table 1). Phenotypes significantly affected by SGE included behavioural (helplessness), physiological (serum LDL cholesterol, healing from an ear punch, blood eosinophils, serum alpha-amylase concentration, blood platelets, acute hypoxic response), and morphological (weight of adrenal glands) traits. Importantly, among the phenotypes significantly affected by SGE were both phenotypes known or expected to be affected by the social environment, namely helplessness (a murine model for depression), blood eosinophils (a measure of immunity) and weight of adrenal glands (a measure associated with stress), and phenotypes less expected to be socially affected, such

121 as LDL levels, response to hypoxia, and healing from an ear punch. Notably, the
122 significant and substantial SGE detected in this population for healing from an ear
123 punch (P = 0.00018, variance explained by SGE in aggregate = 17 +/-4%) constitute
124 the third independent line of evidence that SGE affect wound healing in laboratory
125 mice(5). Altogether, our results demonstrate that SGE may affect a broad range of
126 phenotypes including traits not *a priori* expected to be socially affected, which is
127 consistent with prior evaluation of SGE in other populations(5).
128
129 **Correlation between SGE and DGE loci acting on the same phenotype**
130 The polygenic model used for variance decomposition fits a correlation coefficient ρ
131 (See Methods) that quantifies the extent to which SGE and DGE acting on the same
132 phenotype arise from similar loci. We stress that, in this section and throughout the
133 manuscript, we compare SGE and DGE *acting on the same phenotype* (but do this for
134 all phenotypes). Using simulations, we observed that ρ can be accurately estimated,
135 provided the aggregate contribution of SGE and DGE is sufficiently large
136 (Supplementary Figure 1). Consequently, we limited the analysis of ρ to 28
137 phenotypes for which both aggregate SGE and aggregate DGE explained at least 5%
138 of phenotypic variation. The SGE-DGE correlation coefficient ρ varied between -0.28
139 and 1 across these traits, with an average of 0.42 (Figure 2 and Supplementary Table
140 1). For 10 out of the 28 phenotypes ρ was significantly different from zero (nominal P
141 < 0.05, Figure 2 and Supplementary Table 1), indicating that loci exist that influence
142 both the phenotype of the focal animal (DGE) and the same phenotype of cage mates
143 (SGE). Strong evidence for shared SGE and DGE loci ($\rho \neq 0$ at Bonferroni-corrected
144 P < 0.05) was observed for healing from an ear punch, weight of adrenal glands, serum
145 LDL cholesterol levels, and mean platelet volume.
146 We also evaluated evidence that $|\rho|$ was different from one (i.e. ρ different from
147 one and minus one) in order to empirically evaluate the widely-influential model of
148 "phenotypic contagion". Phenotypic contagion or "spread" is a model for social effects
149 whereby the phenotype of interest of a focal individual is affected by the same
150 phenotype of their social partners. In humans, cognitive susceptibility to depression,
151 alcohol consumption, stress, obesity and educational attainment, for example, have
152 been suggested to be "contagious" or "spread" across college roommates, spouses,
153 friends, or parent/offspring(6, 11, 12, 21-25). 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(26). Here we leveraged the parameter ρ to test whether phenotypic contagion was sufficient to account for SGE: under a model of pure phenotypic contagion, |ρ| is expected to be equal to one; on the contrary, if traits of social partners other than the phenotype of interest mediate social effects, |ρ| is expected to be different from one. We found that |ρ| was significantly different from one (nominal P < 0.05) for 10 out of 28 phenotypes (Figure 2 and Supplementary Table 1), with strong evidence (P < 0.05 after Bonferroni correction) for helplessness and healing from an ear punch. Our results empirically demonstrate that traits of social partners other than the phenotype of interest may be important, even when some level of contagion is likely, and motivate the use of sgeGWAS to uncover such traits.

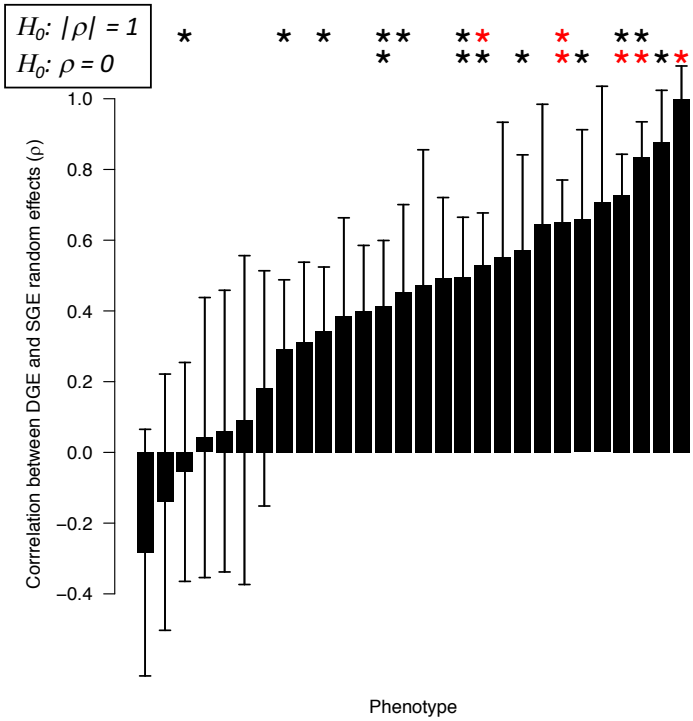


Figure 2 *Correlation coefficients ρ between SGE and DGE random effects (see Methods). Shown are correlation coefficients for 28 phenotypes with error bars denoting standard errors. The stars denote significance for rejecting H_0: $\rho = 0$* (i.e. SGE and DGE arise from different loci, bottom row) and *H_0: $|\rho| = 1$ (i.e. pure phenotypic contagion, top row). Black stars (*) denote nominal P value < 0.05, red stars (*) denote Bonferroni-corrected P value < 0.05.*

174

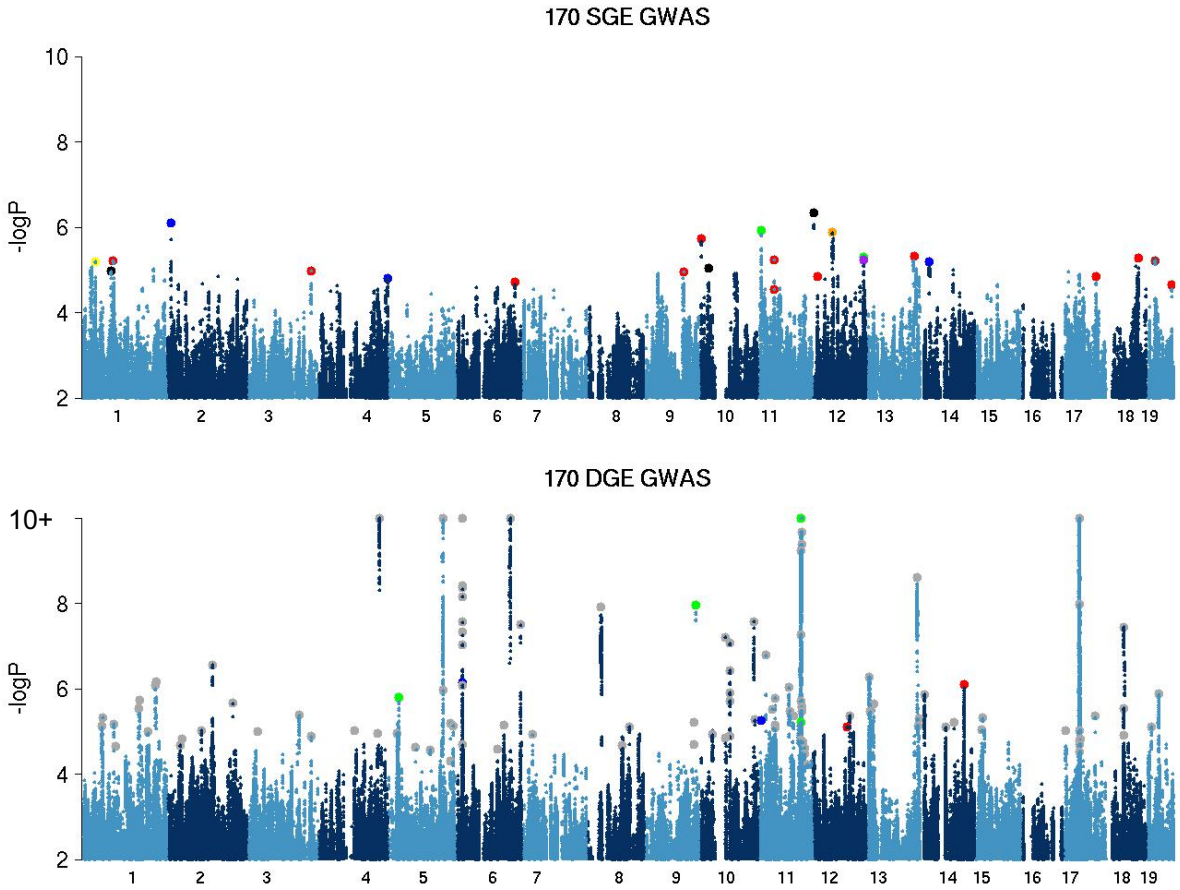
175 **sgeGWAS and dgeGWAS of 170 phenotypes**

176 To map SGE, we calculated the "social genotype" of a mouse at a variant as the sum
177 of the reference allele dosages across its cage mates at the variant(17, 18), and tested
178 for association between social genotype and phenotype. In order to avoid spurious
179 associations, we accounted for background SGE, DGE and non-genetic effects using
180 random effects as in the model used for variance decomposition. In the sgeGWAS we
181 also accounted for DGE of the tested variant, by including direct genotypes at the
182 variant as a covariate (See Methods). Similarly, in the dgeGWAS we included social
183 genotypes at the variant as a covariate. We hereafter refer to this strategy as
184 "conditioning". We found that conditioning was necessary to avoid spurious
185 associations in the sgeGWAS due to co-localised DGE (Supplementary Figure 2). As
186 we show in the Supplementary Note, this problem originates from the use of each
187 mouse as both focal individual and cage mate in the analysis, a strategy that has been
188 used before to maximise sample size when all individuals are phenotyped and
189 genotyped(17, 18). Importantly, spurious associations may arise even if all individuals
190 are strictly unrelated (Supplementary Note). A power analysis suggested that
191 conditioning may slightly decrease power to detect SGE in the absence of co-localised
192 DGE, particularly when direct and social genotypes are highly correlated
193 (Supplementary Figure 3a and 3c) but would increase power if the locus also gave
194 rise to DGE (Supplementary Figures 3b and 3d).

195 In order to compare, for each phenotype, the results of sgeGWAS and
196 dgeGWAS, we defined a locus as the average size of the 95% confidence interval in
197 this population, namely 1.5Mb(19), and, following Nicod et al.(19), used a per-
198 phenotype FDR approach to account for multiple testing (see Methods). sgeGWAS
199 identified 24 genome-wide significant loci for 17 of the 170 phenotypes (FDR < 10%;
200 Figure 3 and Supplementary Table 2). In comparison, dgeGWAS identified 120
201 genome-wide significant loci for 63 phenotypes at the same threshold (Figure 3 and
202 Supplementary Table 3).

203 There was no overlap between genome-wide significant SGE and DGE loci
204 *acting on the same phenotype*. However, variants at genome-wide significant SGE
205 loci were enriched in small P values in the corresponding dgeGWAS (Supplementary
206 Figure 4). Together these results suggest a partially distinct basis for SGE and DGE

207 *acting on the same phenotype* (i.e. partially different loci and/or effect sizes), which is
208 consistent with the results from the analysis of the correlation parameter ρ.

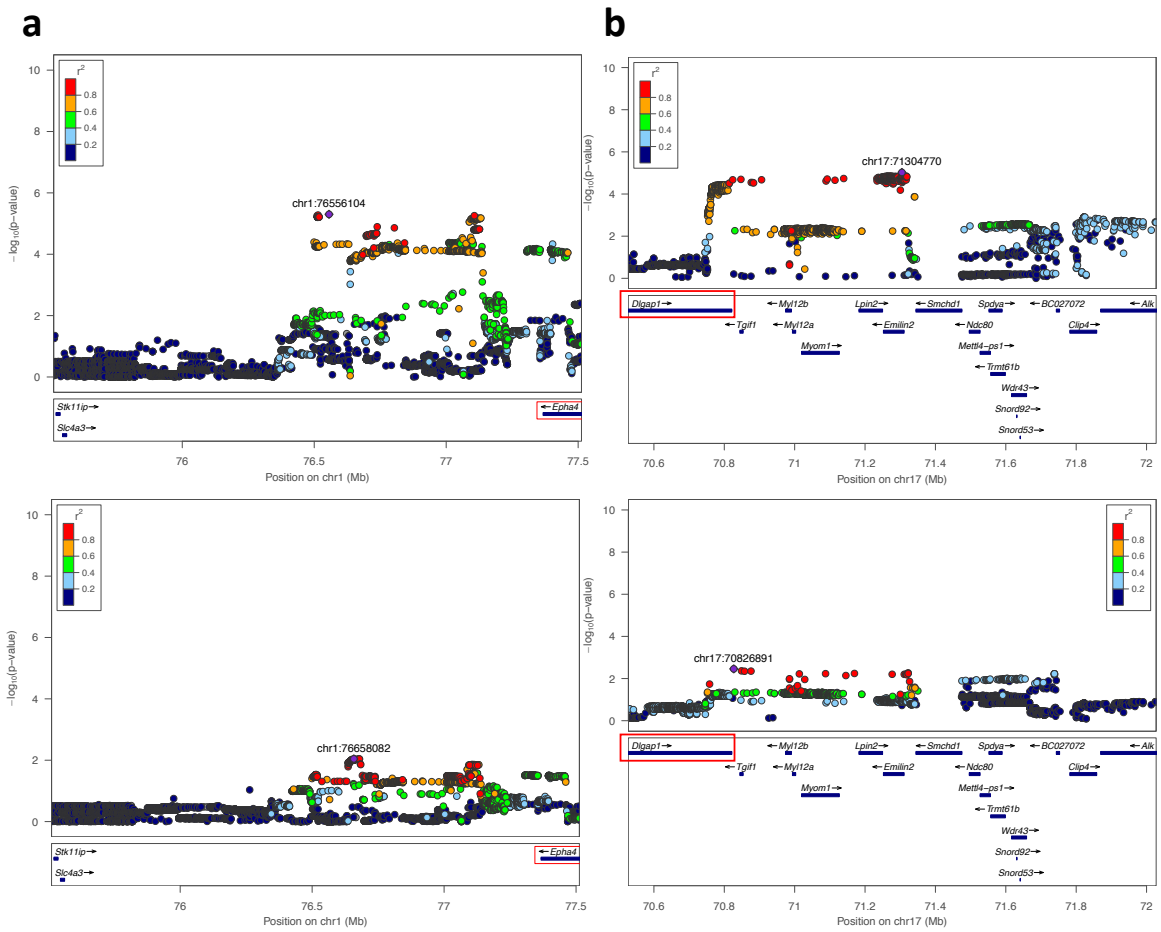


209

210 ***Figure 3*** *Superimposed manhattan plots corresponding to to sgeGWAS (top panel)*
211 *and dgeGWAS (bottom panel) for 170 phenotypes. DGE associations with a negative*
212 *log P value greater than 10 were truncated at this threshold (as indicated by 10+); data*
213 *points with negative log P values smaller than 2 are not shown. Lead variants for all*
214 *genome-wide significant SGE and DGE loci are represented with a larger dot. In the*
215 *SGE panel, each color corresponds to a class of phenotypes: behavioural (red,*
216 *includes 7 behavioural phenotypes with a detected SGE locus), adult neurogenesis*
217 *(black, 2 phenotypes), immune (orange, 1 phenotype), haematological (yellow, 1*
218 *phenotype), blood biochemistry (blue, 2 phenotypes), bone phenotypes (green, 2*
219 *phenotypes), heart function (brown, 1 phenotype), and lung function (purple, 1*
220 *phenotype). In the DGE panel, a genome-wide significant locus is colored grey when*
221 *the corresponding phenotype does not have a genome-wide significant SGE*
222 *association; when the corresponding phenotype does have a genome-wide significant*
223 *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, which facilitates identification of candidate genes at associated loci(19, 27). At each genome-wide significant SGE locus we reran the association analysis using the full set of variants (rather than the pruned set used for GWAS) and prioritized candidate genes that were underneath or closest to the most significantly associated genomic segment, excluding certain categories of genes of unknown function (see Methods). This resulted in five genome-wide significant SGE loci with a single candidate gene (Supplementary Table 2).

An example is an SGE locus on chromosome 1 (Figure 4a, top panel) for immobility in the first two minutes of the Porsolt swim test, a measure of helplessness in CFW mice(28). *Epha4*, the candidate gene at this locus, is critical for the development of the central nervous system (CNS) and synaptic plasticity in the adult brain(29). *Epha4* mutant mice show a range of altered phenotypes including abnormal CNS morphology, altered limb coordination and lower locomotor activity, lower reproductivity, and poor maternal nurturing(30). *Epha4* has also been associated with helplessness(31, 32), but we found little evidence of DGE from *Epha4* on helplessness in our study (Figure 4a, bottom panel), in contrast with strong evidence of SGE. Expression data from the hippocampus of an independent sample of CFW mice(33), mined using Genenetwork(34) (see Methods), and a second genome-wide significant locus for helplessness in our study, located on chromosome 17, helped decipher the pathways mediating the social effects of *Epha4*: of the eight genes prioritized as candidate genes at the chromosome 17 locus (Figure 4b, top panel), one, *Dlgap1*, is among the ten genes whose expression in the hippocampus is most strongly correlated with that of *Epha4*. Thus, *Epha4* and *Dlgap1* of cage mates are likely involved in a common pathway affecting helplessness of focal mice. *Dlgap1* is a core component of the post-synaptic density and *Dlgap1* knock-out mice show selective deficits in sociability(35). Hence, low sociability of cage mates most likely pathway explaining social effects of *Epha4* and *Dlgap1* on helplessness.


a
b
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chr17:71304770
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chr17:70826891
Position on chr1 (Mb)
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Slc4a3
Epha4
Dlgap1
Myl12b
Lpin2
Smchd1
Spdya
BC027072
Alk
Tgif1
Myl12a
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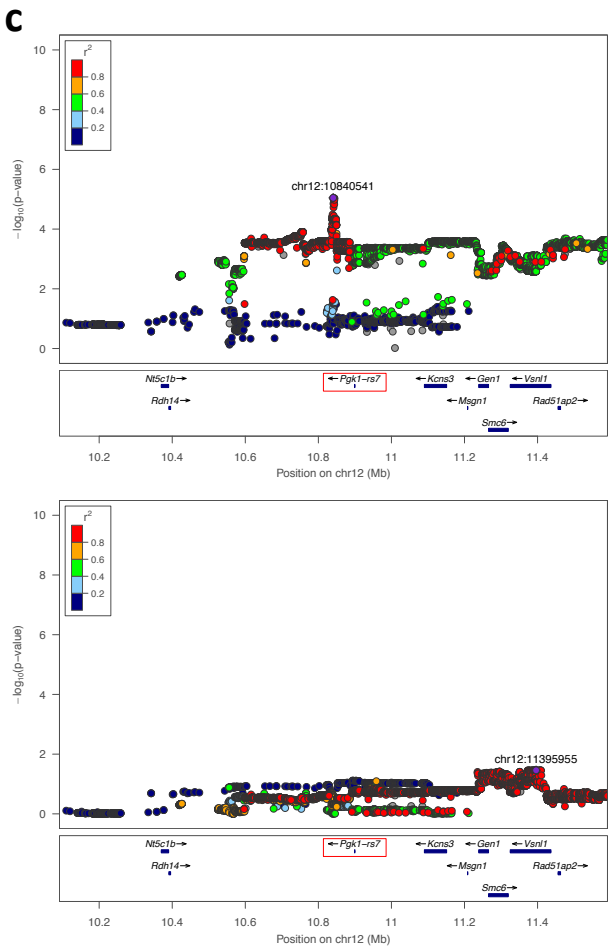

Figure 4 *Locus zoom plots for three genome-wide significant (FDR < 10%) SGE loci. In (a), (b), and (c) the top and bottom panels respectively show SGE and DGE of all variants at the locus. (a) Locus on chromosome 1 for immobility during the first two minutes of the Porsolt swim test, a measure of helplessness and model of depression in mice. Epha4 is the only candidate gene (see Methods) for SGE at this locus. (b) Locus on chromosome 17 for immobility during the last four minutes of the Porsolt swim test. Candidate genes for SGE include Dlgap1, whose expression is highly correlated with that of Epha4 in the hippocampus of CFW mice. (c) Locus on chromosome 12 for a measure of disrupted sleep, where Pgk1-rs7 is the only candidate gene for SGE.*

Among the other genome-wide significant SGE loci with a single candidate gene was a locus on chromosome 12 for a measure of disrupted sleep (Figure 4c, top panel). More precisely, after sharing a cage for 15 weeks mice were singly housed for three days so that their sleep could be recorded; the measure reported here was defined as the sum of differences in hourly sleep times between days 2 and 3(19).

273 Thus, this measure captures unpredictable, disrupted sleep most likely resulting from
274 mice struggling to adapt to their new housing conditions. The candidate gene at this
275 locus, *Pgk1-rs7*, is a pseudogene of phosphoglycerate kinase 1 (*Pgk1*, located on
276 chromosome X). Lack of linkage disequilibrium (see Methods) between variants in the
277 vicinity of *Pgk1-rs7* and variants in the vicinity of *Pgk1* suggests our finding is not the
278 result of sequencing read misalignment during genotyping. The perfect sequence
279 match between the proteins encoded by *Pgk1-rs7* and *Pgk1,* the position of *Pgk1* on
280 the X chromosome, and the existence of a functional pseudogene for the human
281 phosphoglycerate mutase(36) (the enzyme acting on the product of PGK in
282 glycolysis), together suggest that *Pgk1-rs7* might be a functional autosomal substitute
283 for *Pgk1*, a process suggested to have enhanced male germline functions in
284 evolution(37). Neither *Pgk1-rs7* nor *Pgk1* have been associated with sleep and we
285 found no evidence of DGE on sleep at this locus (Figure 4c, bottom panel), suggesting
286 that other traits of cage mates are involved. Given that *Pgk1-rs7* is a marker of brown
287 adipose tissue - the tissue responsible for non-shivering thermogenesis - and that its
288 expression is activated by cold temperatures(38), our hypothesis regarding the
289 pathways mediating social effects of *Pgk1-rs7* on sleep is as follows: first, *Pgk1-rs7*
290 controls the heat produced by a mouse, which in turn determines the need for its cage
291 mates to develop their own thermogenic capacity(39). Indeed mice often huddle in the
292 laboratory because ambient temperature (20° in the initial study) is well below their
293 thermoneutral zone (30° (40)), and warm cage mates reduce the need for one mouse
294 to produce its own heat(39). Secondly, when the mice were separated for the sleep
295 test after several weeks of sharing a cage, those with low thermogenic capacity likely
296 got awaken by the cold conditions, resulting in disrupted sleep. Our results illustrate
297 how the results of sgeGWAS may be used to generate hypotheses as to the traits of
298 social partners mediating social effects.
299
300 **Architecture of SGE and comparison with that of DGE**
301 Despite being carried out on the same individuals and phenotypes, and in a perfectly
302 analogous manner, sgeGWAS identified fewer genome-wide significant loci than
303 dgeGWAS (24 associations for 17 phenotypes and 120 associations for 63
304 phenotypes respectively). One possible reason for this is dilution of social genetic
305 effects occurring when the focal mouse can only interact with one cage mate at a time.

306 We explored this possibility in a power analysis where allelic effects were fixed, three
307 categories of minor allele frequencies (MAF) were considered (low, medium, or high;
308 see Methods), and local DGE or SGE were simulated (see Methods). Briefly, we used
309 two generative models for SGE : an additive model whereby SGE received by a focal
310 mouse correspond to the sum of the genetic effects projected by its cage mates, and
311 an average model, reflecting dilution, whereby SGE received by one mouse
312 correspond to the average of the genetic effects projected by its cage mates. Our
313 results show that power to detect SGE loci always increases with MAF and is higher
314 than power to detect DGE when SGE were simulated under the additive model (Figure
315 5a). When SGE were simulated under the average model, however, power to detect
316 SGE was lower than power to detect DGE. Thus, smaller effect sizes or dilution of
317 social effects may have led to the detection of fewer genome-wide significant SGE
318 associations compared to DGE associations.

319 Genome-wide significant SGE associations generally explained less
320 phenotypic variance than genome-wide significant DGE associations: SGE
321 associations explained a maximum of 2.5% of phenotypic variance, while eleven
322 genome-wide significant DGE associations explained more than 5% of phenotypic
323 variance and up to 40% (Figure 5b, Supplementary Table 2 and Supplementary Table
324 3); average values across all genome-wide significant associations were 1.8% for
325 SGE and 2.7% for DGE.

326 Contrastingly, we found that genome-wide significant associations explained a
327 similar proportion of the corresponding genetic variance for SGE and DGE (Figure 5c).
328 More precisely, across 5 phenotypes with aggregate contribution of SGE greater than
329 5% and at least one genome-wide significant SGE association, we found that an
330 average of 32.5% of the aggregate variance was explained by genome-wide
331 significant associations. For DGE, that figure was calculated across 55 phenotypes
332 and was equal to 32.1%. The proportion of aggregate variance explained by genome-
333 wide significant associations may seem large given the relatively small number of
334 genome-wide significant associations per phenotype (e.g. compared to humans(41)),
335 but is consistent with studies of DGE in other outbred laboratory rodent
336 populations(42, 43) and are the result of a relatively small number of variants
337 segregating in the CFW population and relatively high MAFs(19). Our quantification of
338 the proportion of genetic variance explained by genome-wide significant associations
339 suggests SGE and DGE likely have similar levels of polygenicity. However, given the

small number of phenotypes where this fraction could be calculated, this conclusion will need to be re-evaluated when more SGE associations are discovered in other datasets.

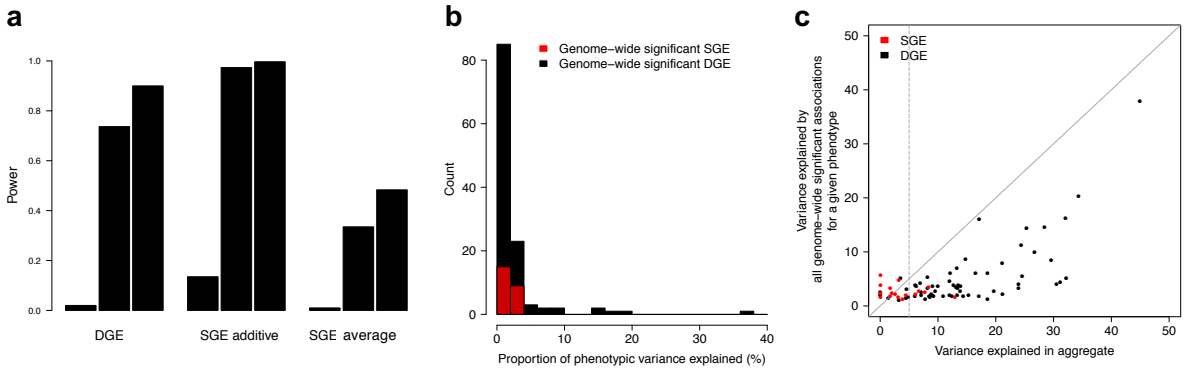

Figure 5 *Power to detect local SGE and DGE, and characterisation of the architecture of SGE and DGE. (a) Power to detect local genetic effects in simulations. Three types of local genetic effects were simulated: DGE, SGE arising from additive genetic effects across cage mates, and SGE arising from average genetic effects across cage mates (see main text and Methods). 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). Power was calculated at a* genome-wide significance threshold of negative log P 5. *(b) Histogram of the proportion of phenotypic variance explained by individual genome-wide significant SGE (red) and DGE (black) associations (FDR < 10%). (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 associations (y axis). Each dot corresponds to a phenotype with at least one genome-wide significant association. Only those phenotypes with aggregate SGE (or DGE) > 5% were considered to calculate the average values reported in the main text.*

Discussion

In this study we performed the comparative analysis of SGE and DGE acting on a broad range of phenotypes measured in outbred laboratory mice. For each phenotype we applied GWAS as well as variance decomposition techniques to identify individual loci giving rise to SGE in the CFW mouse population and compare the architecture of

368 SGE to that of DGE. Our results demonstrate that sgeGWAS may be used to identify
369 novel genetic loci that contribute to inter-individual differences, illustrate how such loci
370 can help infer the traits of social partners that affect the phenotype of interest, and
371 suggest comparatively larger sample sizes will be necessary required for sgeGWAS
372 compared to dgeGWAS.

373 For this study we chose to investigate not only phenotypes expected to be
374 affected by social partners, such as behaviours and immune traits, but also
375 phenotypes that were not *a priori* known or suspected to be socially affected, such as
376 lung response to hypoxia, and muscle and bones characteristics. Indeed, our previous
377 work, based on two different populations of mice(5), had suggested that SGE could
378 affect a broad range of behavioural, physiological and morphological phenotypes. In
379 this study we found that serum LDL cholesterol and alpha-amylase (a marker of
380 pancreatic function), blood platelets, acute hypoxic response and healing from an ear
381 punch, in addition to a number of behavioural and immune phenotypes, were
382 significantly affected by SGE in aggregate (FDR < 10%, Supplementary Table 1).
383 Thus, our study identified several phenotypes not previously known to be affected by
384 the social environment and confirmed that SGE can affect a broad range of
385 phenotypes. While the exact phenotypes affected by SGE in different populations
386 vary, presumably due to differences in the pool of genetic variants segregating in the
387 populations and other experimental variables(5), healing from an ear punch shows
388 remarkable consistency across populations: it is indeed significantly and strongly
389 affected by SGE, in aggregate, in all three mouse populations we have studied to
390 date(5). Unfortunately, there were no genome-wide significant SGE loci for this
391 phenotype in this study, which prevented identification of the underlying mechanisms.

392 Our analysis of a broad range of phenotypes, together with testing of genome-
393 wide variants, was also meant to provide a view of the architecture of SGE that is as
394 unbiased as possible. We identified far fewer genome-wide significant SGE loci
395 compared to DGE loci (24 and 120 respectively, Figure 3) and found that SGE loci
396 tended to explain less phenotypic variation than DGE loci for the same phenotype
397 (Figure 5b). Our results contrast with findings from two early mapping studies of SGE,
398 which identified more SGE loci and found greater effect sizes for SGE loci as
399 compared to DGE loci(15, 17). This discrepancy could be due to differences in the
400 phenotypes studied, but more likely arises from the fact that one of those studies
401 tested loci with genome-wide significant DGE only and the other one failed to account

402 for DGE of the tested variant, thus not controlling the type 1 error rate if direct and
403 social genotypes were correlated (as we show in Supplementary Figure 2). Notably,
404 our results are consistent with two other studies that mapped genome-wide SGE and
405 DGE acting on a small set of traits: one that focused on mouse pup behaviour and
406 found similar effect sizes for SGE and DGE loci(4), and one that focused on pecking
407 behaviour in hens and identified DGE loci but no SGE loci(18). Given the breadth of
408 phenotypes considered in our study, lower effect sizes is likely to be a general feature
409 of SGE loci, which implies future sgeGWAS will require larger sample sizes than
410 dgeGWAS to be equally powered.

411 Given the effort that we predict will be necessary to carry out well-powered
412 sgeGWAS, one goal of our study was to empirically evaluate the promise of sgeGWAS
413 to identify genetic loci not identified by dgeGWAS and provide clues on yet unknown
414 traits of social partners affecting the phenotype of interest. To do so, we calculated the
415 correlation ρ between SGE and DGE acting on the same phenotype and tested
416 whether it was different from |1|. We found that for 10 out of 28 phenotypes ρ was
417 statistically different from |1| (nominal $P < 0.05$, Figure 2 and Supplementary Table 1),
418 suggesting that different loci and/or different effect sizes give rise to SGE and DGE.
419 Consistent with this observation, genome-wide significant sgeGWAS and dgeGWAS
420 loci never overlapped. SGE and DGE loci were largely different even for phenotypes
421 with prior evidence of "contagion", such as helplessness(21, 44), a murine model for
422 depression. Hence, our results motivate the use of sgeGWAS to discover more traits
423 of social partners that influence depression and other phenotypes.

424 We focused on two genome-wide significant loci with a single candidate
425 gene and no evidence of DGE to illustrate how sgeGWAS may help identify novel
426 traits of cage mates affecting the phenotype of interest. A locus for helplessness on
427 chromosome 1 featured *Epha4* as single candidate gene (Figure 4a), and we found
428 that *Epha4* expression in the hippocampus of CFW mice was highly correlated with
429 expression of *Dlgap1*, a candidate gene at another genome-wide significant SGE
430 locus for helplessness in our study (Figure 4b). *Epha4* and *Dlgap1* both point to
431 neurobehavioral traits of cage mates affecting helplessness of focal mice, and a report
432 of selective deficits in sociability of *Dlgap1* knock-out mice(35) further indicates
433 sociability of cage mates likely contributes to social effects on helplessness.
434 Consistent with this hypothesis, single housing decreases the effectiveness of

435 antidepressants in Swiss mice(45), which are genetically similar to CFW mice, and
436 social C57BL/6NHsd show increased anhedonia (another model of depression) when
437 housed with less social BALB/cOlaHsd cage mates(46). The other locus we
438 investigated suggested an association between *Pgk1-rs7*, a gene associated with
439 thermogenesis(38), and sleep disruption in cage mates (Figure 4c). We hypothesized
440 that *Pgk1-rs7* controls the heat produced by a mouse, which in turn determines the
441 need for its cage mates to develop their own thermogenic capacity(39, 40) given that
442 mice huddle to stay warm when sleeping; when the mice were singly housed for the
443 sleep test, those with low thermogenic capacity got awaken by the cold conditions,
444 resulting in the observed disrupted sleep. Consistent with this hypothesis, previous
445 studies have described how increased cage density reduces thermogenic capacity
446 even at ambient temperature very close to thermoneutrality (28° in Himms-Hagen et
447 al.(47)) and how sleep quality is impacted by ambient temperatures(48).
448 One limitation of using SGE to study social effects is that it is blind to traits of
449 social partners that are mostly non-genetically determined. Additionally, identifying
450 traits of partners mediating social effect from SGE associations will likely be
451 challenging, for the same reasons as it is challenging to infer "within-body" pathways
452 of phenotypic variation from dgeGWAS results(13, 49). Additional data such as
453 expression data collected in the cage mates (where SGE originate) may help improve
454 the prioritization of candidate genes at SGE loci and identify the most relevant tissues.
455 Finally, our study makes several important methodological contributions that
456 will help perform sgeGWAS, particularly in outbred populations where both DGE and
457 SGE contribute to phenotypic variation. Specifically, we described the determinants of
458 power for SGE and highlighted how dilution can reduce power to detect SGE (Figure
459 5a). We also showed how using the same individuals as both focal individuals and
460 cage mates in the analysis leads to correlations between direct and social genotypes
461 at a locus, which need to be accounted for to avoid spurious associations
462 (Supplementary Note and Supplementary Figure 2). Similar correlations between
463 direct and social genotypes, but potentially much stronger, may arise for different
464 reasons in other datasets, notably when focal individuals and social partners are
465 related, or as a result of direct assortments (e.g. assortative mating(50, 51), homophily
466 between friends(6)). Our analysis approach is robust to spurious associations that
467 arise in such situations.

468
469 **Conclusions**
470
471 Our study sheds light on a new axis of genetics, namely genetics effects on an
472 individual's phenotype that arise from genotypes of social partners (SGE). Our results
473 vastly improves our understanding of the architecture of SGE, and illustrate how SGE
474 loci may provide insights into the mechanisms of social effects. Our results will enable
475 future sgeGWAS by guiding their design, analysis, and interpretation.
476
477
478 # Methods
479
480 *Phenotypes and experimental variables*
481
482 Phenotypes and experimental variables (covariates) for 1,934 Crl:CFW(SW)-US_P08
483 (CFW) mice were retrieved from http://wp.cs.ucl.ac.uk/outbredmice/. Phenotypes
484 were normalized using the boxcox function (MASS package(52)) in R; phenotypes that
485 could not be normalised satisfactorily (transformation parameter lambda outside of -2
486 to 2 interval) were excluded. The subset of covariates used for each phenotype is
487 indicated in Supplementary Table 1. Because data for some phenotypes were missing
488 for some mice, the sample size varied. The sample size for each phenotype after all
489 filtering (see below) is indicated in Supplementary Table 1.
490
491 *Caging information*
492
493 Mice were four to seven weeks old when they arrived at the phenotyping facility. They
494 were grouped with their cage mates and then spent nine to twelve weeks undisturbed
495 in quarantine. They spent a further four weeks together during phenotyping. Males
496 were housed with males and females with females.
497 Cage assignments were not included in the publicly available dataset but were
498 provided by the authors upon request and are now provided in Supplementary Table
499 4. Cage assignments were recorded at eleven time points throughout the study and
500 showed that a few mice were taken out of their original cages and singly housed,

501 presumably because they were too aggressive to their cage mates. When this
502 happened, we excluded all the mice in that cage from the analysis. We also excluded
503 cages where some of the mice were "genetically close" (as defined below) to many
504 other mice. Finally, we only retained cages with exactly three mice per cage. Although
505 from the sleep test on all mice were singly housed, we still investigated "persistent"
506 SGE on sleep and tissue phenotypes (persistence over one day for sleep phenotypes
507 and over a few days for tissue measures).
508
509 *Genome-wide genotypes*
510
511 From http://wp.cs.ucl.ac.uk/outbredmice/ we retrieved both allele dosages for 7 million
512 variants and allele dosages for a subset of 353,697 high quality, LD-pruned variants
513 (as described in Nicod et al.(19)). We used high quality, LD-pruned variants for all
514 analyses but the identification of candidate genes at SGE loci (see below), for which
515 we used the full set of variants.
516
517 *Genetic relatedness matrix (GRM) and exclusion of "genetically close" mice*
518
519 The genetic relatedness matrix was calculated as the cross-product of the LD-pruned
520 dosage matrix after standardizing the dosages for each variant to mean 0 and variance
521 1.
522 We excluded whole cages of mice based on GRM values as follows: we defined
523 a "close pair" of mice as having a GRM value greater than 0.3 (based on the histogram
524 of all GRM values). 199 mice in 145 cages were involved in such close pairs. Excluding
525 all 145 cages would have resulted in excluding 435 mice out of a total of 1,812, which
526 would have led to substantially reduced power for sgeGWAS and dgeGWAS. Thus,
527 we made a compromise and only excluded the 19 cages that were involved in 4 or
528 more close pairs (57 mice excluded).
529
530 *Variance decomposition*
531
532 The same method as described in details in Baud et al.(5) was used. Briefly, the model
533 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:

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

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

$+ (ZI^T)_{i,j}$ }Error! Bookmark not defined. Error! Bookmark not defined. $+ \sigma^2_{E_S}(ZIZ^T)_{i,j}$

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

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 $P = I - \frac{11'}{n}$ (53, 54).

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(55). Significant SGE contributions were reported at FDR < 10% (corresponding to Q value < 0.1).

Correlation between DGE and SGE

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

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

with ρ reflecting 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. The parameter 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 |ρ| was significantly different from 1 using a one-degree of freedom LLR test.

Simulations for Supplementary Figure 1.

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, σ^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

592 the simulations was calculated and used to calculate "realised" simulation parameters
593 from the "target" parameters above. The realised parameters were used for
594 comparison with the parameters estimated from the simulations.
595
596 *Definition of "social genotype" for sgeGWAS*
597
598 In the sgeGWAS, we assumed additive effects across cage mates and calculated the
599 "social genotype" of a mouse as the sum of the reference allele dosages of its cage
600 mates. The same assumptions were made by Biscarini *et al.*(17) and Brinker *et al.*(18).
601
602 *Correlation between direct and social genotypes at a variant*
603
604 Spearman's rank correlation coefficient was used. We tested whether the correlation
605 was different from 0 using the function cor.test in the R package stats(56).
606
607 *Models used for sgeGWAS and dgeGWAS*
608
609 To test SGE of a particular variant, we compared the following two models:
610
611 $y_f = X_f\underline{b} + a_{D,f} + e_{D,f} + Z_f\underline{a_S} + Z_f\underline{e_S} + W_f\underline{c} + G_f b_D$ (1, null)
612
613 $y_f = X_f\underline{b} + a_{D,f} + e_{D,f} + Z_f\underline{a_S} + Z_f\underline{e_S} + W_f\underline{c} + G_f b_D + Z_f G b_S$ (2, alternative)
614
615 Here, G is the vector of direct genotypes at the tested variant, b_D the estimated
616 coefficient for local DGE and b_S the estimated coefficient for local SGE.
617 The models were fitted using LIMIX(57, 58) with the covariance of the model estimated
618 only once per phenotype, in the null model with no local genetic effect (model 0).
619 The significance of local SGE was calculated by comparing models (1) and (2) with a
620 1-degree of freedom LLR test.
621 We refer to the inclusion of $G_f b_D$ in model (1, null) as "conditioning".
622
623 dgeGWAS was carried out by comparing model (2) above to the null model (3) below:
624 $y_f = X_f\underline{b} + a_{D,f} + e_{D,f} + Z_f\underline{a_S} + Z_f\underline{e_S} + W_f\underline{c} + Z_f G b_S$ (3, null)

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

626

627 *Identification of genome-wide significant associations*

628

629 Because we wanted to compare the architecture of DGE and SGE *for each phenotype*
630 *independently*, we adopted the per-phenotype FDR approach used by Nicod et al.(19).
631 In contrast to a study-wise FDR, this approach enables the direct comparison of paired
632 SGEwas and DGEwas for the same traits.

633 The procedure we used to control the FDR accounts for the fact that we report
634 loci rather than individual variants(59), where a locus is defined as the 1.5 Mb-wide
635 window around a SNP (this window size is the average 95% confidence interval for
636 DGE QTLs in (19)). More precisely, for each phenotype and for each type of genetic
637 effect (social and direct), we performed 100 "permuted GWAS" by permuting the rows
638 of the matrix of social (respectively direct) genotypes, and testing each variant at a
639 time using the permuted genotypes together with the un-permuted phenotypes,
640 covariates, GRM and matrix of direct (respectively social) genotypes (for conditioning).
641 See (58, 60) for references on this permutation approach. For a given P value x, the
642 per-phenotype FDR can be calculated calculated as:

643 $$FDR(x) = \frac{\#\ loci\ with\ P < x\ in\ permuted\ data}{100\ \times\ \#\ loci\ with\ P < x\ in\ unpermuted\ data}$$

644

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

646

647 *Definition of candidate genes at associated loci*

648

649 At each significantly associated locus we defined a 1.5Mb window centred on the lead
650 variant, identified all the variants that segregate in this window based on the full set of
651 7M variants, and reran the sgeGWAS and dgeGWAS locally with all the variants at
652 the locus. We highlighted those genes that are located within the most significantly
653 associated segments and whose MGI symbol does not start by 'Gm', 'Rik', 'Mir', 'Fam',
654 or 'Tmem' in order to focus on genes with known function and generate more tractable
655 hypotheses on the pathways of social effects.

656

657 *Gene expression in the hippocampus of an independent sample of CFW mice*

Gene expression in the hippocampus of an independent sample of 79 male CFW mice, initially published in parker et al.(33), was available from GeneNetwork (http://gn2.genenetwork.org/). The data are accessible by selecting Mouse as *Species*, CFW Outbred GWAS as *Group*, Hippocampus mRNA as *Type*, and UCSD CFW Hippocampus (Jan17) RNA-Seq Log2 Z-score as *Dataset*. To retrieve the genes whose expression is most highly correlated with that of *Epha4*, we entered Epha4 in the *Get Any* field. Following selection of the Epha4 Record, we used *Calculate Correlations* with Sample r as *Method*, UCSD CFW Hippocampus (Jan17) RNA-Seq Log2 Z-score as *Database*, and Spearman rank as correlation *Type*.

Calculation of linkage disequilibrium between variants in the vicinity of Pgk1-rs7 and variants in the vicinity of Pgk1

Dosages at LD-pruned variants in the regions chr12:10,091,326-11,591,326 and chrX: 105,500,000- 106,500,000 were used as input for PLINK2 to generate binary PLINK files, and linkage (R^2) was subsequently calculated between all pairs of variants.

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:

692 $$\frac{var(Gb_D)}{\sum var(X_c b_c) + \sum var(Gb_D) + \sum var(ZGb_S) + sampleVar(C)}$$

691

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

695

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

700 $$\frac{\sum var(ZGb_S)}{\sum var(X_c b_c) + \sum var(Gb_D) + \sum var(ZGb_S) + sampleVar(C)}$$

699

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

704

706 $$\frac{\sum var(Gb_D)}{\sum var(X_c b_c) + \sum var(Gb_D) + \sum var(ZGb_S) + sampleVar(C)}$$

705

707 *Simulations for Supplementary Figure 2c and 2d.*

708

709 Phenotypes were simulated based on the genotypes and cage relationships of the
710 1,812 mice. Phenotypes were simulated as the sum of random effects and local DGE
711 (from model (1)), with the following parameters: $\sigma^2_{A_D} = 5$ or 20, $\sigma^2_{A_S}$ = 5 or 20, $\rho_{A_{DS}}$= 0.5,
712 $\sigma^2_{E_D}$= 30, $\sigma^2_{E_S}$= 30, $\rho_{E_{DS}}$ = -0.97, σ^2_C = 25. The values for $\rho_{A_{DS}}$, $\sigma^2_{E_D}$, $\sigma^2_{E_S}$, $\rho_{E_{DS}}$, and σ^2_C
713 were close to the median of the corresponding estimates from the real data. $\sigma^2_{A_D} = 5$
714 and $\sigma^2_{A_S} = 5$ correspond to low polygenic effects in the real data, and $\sigma^2_{A_D} = 20$ and
715 $\sigma^2_{A_S} = 20$ correspond to high polygenic effects in the real data. We simulated local
716 DGE at random variants in the genome, and simulated variances of 0, 5, 20 or 50.
717 The results we show in Supplementary Figure 2c and 2d are based on a subset
718 of simulations: $\sigma^2_{A_D} = 20$ and $\sigma^2_{A_S} = 20$ and local DGE variance of 20.

719

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

721

722 Phenotypes were simulated based on the real genotypes but random cages.
723 Phenotypes were simulated as the sum of random effects, local DGE and local SGE
724 (model (2)) with the following parameters: $\sigma^2_{A_D}$ = 17, $\sigma^2_{A_S}$ = 17, $\rho_{A_{DS}}$= 0.65, $\sigma^2_{E_D}$= 19,
725 $\sigma^2_{E_S}$= 15, $\rho_{E_{DS}}$ = -0.8, σ^2_C = 25. Those values correspond to the median estimates for
726 phenotypes with aggregate SGE and DGE > 0.1.

727 We simulated local SGE and DGE at variants where direct and social
728 genotypes were either lowly correlated (Spearman correlation negative log P value <
729 0.05) or more highly correlated (Spearman correlation negative log P value > 0.2), and
730 had with low MAF (MAF < 0.05), medium MAF (0.225<MAF<0.275) or high MAF
731 (MAF>0.45). We simulated local DGE with an allelic effect of 0 or 1 (1 corresponds to
732 a large effect in the real data). We simulated local SGE under two alternative
733 generative models: an "additive" model by using Z as in model (2) (i.e. filled with 0s
734 and 1s) or a "proportional" model by using $Z' = {}^{Z}/_{N}$. In all cases we simulated an
735 allelic effect of 0.2 (similar to the average allelic effect estimated in the SGE GWAS).
736 The sample variance of the simulated local DGE term is $var(Gb_D) = 2p(1-p)\, b_D^2$; it
737 is $var(ZGb_S) = 2\mathrm{N}p(1-p)\, b_S^2$ for the local SGE term simulated under the additive
738 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
739 under the proportional model.

740

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

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

748

749 *Scripts used in this study*

750

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

753

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