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Assessing pleiotropy and its evolutionary consequences: pleiotropy is not necessarily limited, nor need it hinder the evolution of complexity

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In a Review in this journal (The pleiotropic structure of the genotype–phenotype map: the evolvability of complex organisms. *Nature Reviews Genetics* **12**, 204–213 (2011))[1], Wagner and Zhang concluded from their analyses of effects of mutant genes that most genes only affect a small number of traits: "In summary, overwhelming empirical data, from unicellular eukaryotes such as yeast to complex vertebrates such as humans and mice, show that pleiotropy is generally low"[1]. Understanding the extent of pleiotropy is important, not least when considering opportunities for evolution, because the more pleiotropic the effects of a gene are, the more likely the gene is to affect the phenotype of some trait unfavourably and hence the more likely it is to inhibit evolutionary change. This relationship is formalized in Fisher's geometric model[2].

We have recently considered alternative interpretations of Wagner and Zhang's results[1,3], and we find the evidence for limited pleiotropy less convincing[4]. In particular, these authors declared genes to have a pleiotropic effect on a trait only if the effect achieved statistical significance for that trait — the threshold was usually set high to allow for multiple comparisons[1,3]. As described in REF. 4 and in TABLE 1, we modelled the correlated effects of genes on traits under two types of distribution in the presence of normal experimental sampling errors. As expected, the mean number of detected traits falls as the significance threshold rises relative to the standard deviation of trait effects (TABLE 1). Importantly, the mode of the number falls as the correlation of gene effects among traits increases because, for the limited number of genes with the largest effects, many traits are detected, but for most genes only very few traits are detected. In a model in which gene effects are assumed to have a modular structure, the mode is much less sensitive to correlations of gene effects among genes in the same module. Thus, the more highly correlated the overall gene effects are, the less likely pleiotropy is to be seen[4].

Table 1 | **Correlated effects of genes on traits under two types of distribution**

(r_a, r_e)	Normal distribution		Wishart distribution	
	5% threshold	0.2% threshold	5% threshold	0.2% threshold
$\sigma_a = 2$				
(0.0, 0.0)	37	17	26	12
(0.5, 0.0)	28	8	16	4
(0.5, 0.5)	23	6	12	3
(0.75, 0.0)	19	3	9	1
(0.9, 0.0)	12	1	7	1
$\sigma_a = 1$				
(0.0, 0.0)	17	2	14	3
(0.5, 0.0)	12	1	9	1
$\sigma_a = 3$				
(0.0, 0.0)	53	34	35	20
(0.5, 0.0)	43	21	23	9

The table shows the influence of correlations of gene effects (r_a) and sampling error (r_e) on the mode of numbers detected for 100 traits tested. The mean numbers detected do not depend on the correlations. For example, for $\sigma_a = 2$ (where σ_a is the ratio of standard deviation of gene effects to standard deviation of sampling error effects), the mean numbers are, in order, 38.0, 16.7, 25.4 and 12.2. The Wishart distribution has been reflected to be symmetric about zero.

Therefore, deeper statistical analyses are required to assess levels of pleiotropy. For example, subsequent thresholds could be lowered for genes that have a significant effect on any trait at the initial experiment-wide threshold. More information can be gained by analysing the quantitative data directly.

Wagner and Zhang[1] also argue that the more pleiotropic loci have larger effects; however, our model indicates that these apparently larger effects can also be caused by correlated effects among traits[4]. Furthermore, even if there is a rather weak modular structure of gene effects, it can exhibit an apparently strong modular structure using gene-network type analysis.

Although it is clear that pleiotropy inhibits the maintenance of quantitative genetic variation in populations (for an example, see REF. 5), it may not always inhibit the maintenance of genetic variation in fitness and thus the evolution of complexity[6]. The analysis presented in REF. 7 shows that genetic variance maintained in fitness is a U-shaped function of pleiotropy, implying that higher pleiotropy facilitates evolution. Furthermore, based on the conclusion that genes that show higher pleiotropy have larger per-trait effects, Wang *et al.*[3] have argued that pleiotropy can, in fact, promote the evolution of complexity.

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doi:10.1038/nrg2949-c1
Published online 21 February 2012

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Competing interests statement
The authors declare no competing financial interests.