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Correlational selection in the age of genomics

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Ecologists and evolutionary biologists are well aware that natural and sexual selection do not operate on traits in isolation, but instead act on combinations of traits. This long-recognized and pervasive phenomenon is known as multivariate selection, or—in the particular case where it favours correlations between interacting traits—correlational selection. Despite broad acknowledgement of correlational selection, the relevant theory has often been overlooked in genomic research. Here, we discuss theory and empirical findings from ecological, quantitative genetic and genomic research, linking key insights from different fields. Correlational selection can operate on both discrete trait combinations and quantitative characters, with profound implications for genomic architecture, linkage, pleiotropy, evolvability, modularity, phenotypic integration and phenotypic plasticity. We synthesize current knowledge and discuss promising research approaches that will enable us to understand how correlational selection shapes genomic architecture, thereby linking quantitative genetic approaches with emerging genomic methods. We suggest that research on correlational selection has great potential to integrate multiple fields in evolutionary biology, including developmental and functional biology, ecology, quantitative genetics, phenotypic polymorphisms, hybrid zones and speciation processes.

Organisms are functionally integrated adaptive systems, where interactions among traits make the whole more than the sum of its parts. How and why did such functional integration evolve, and what are the evolutionary consequences of genetic correlations between traits? These questions have occupied evolutionary biologists for decades, resulting in a rich but scattered scientific literature on topics such as modularity[1], evolvability[1–3], multivariate selection on trait combinations[4–8] and the evolution of genetic correlation structure[9–12]. Early theoretical work[4,13] predicted that genetic correlations between traits should become aligned with the direction of selection on trait combinations. This important insight made it possible to connect correlational selection (selection on trait combinations rather than traits in isolation; see formal definition in Box 1) to the field of evolutionary quantitative genetics, with its focus on genetic correlation structures. A central testable prediction was adaptive alignment between genetic correlations and the direction of correlational selection, although genetic correlations will also be influenced by other evolutionary forces (for example, mutation and genetic drift) and ecological factors (for example, fluctuating environmental conditions)[9,10].

Correlational selection forms a nexus between several traditionally separate research fields, including ecology and developmental biology (Fig. 1). Correlational selection links organismal level features, such as function and development, both to population phenomena such as modularity and genetic correlation structure and to underlying processes such as natural and sexual selection, which typically arise from interactions with mates, predators, mutualists or the abiotic environment (Fig. 2). These connections have not always been developed explicitly, with the result that whole research fields have largely remained separate, partly due to different terminologies. For instance, in a highly influential review about the evolution of modularity[1], correlational selection was not explicitly mentioned, and instead the authors used the terms modular selection and a modular trait architecture as an expected outcome of selection. Correlational selection can either strengthen or weaken correlations between traits, depending on ecological context. For instance, plant evolutionary biologists studying floral pollination syndromes have noted that mutualistic interactions between pollinators and plants may lead to adaptive decoupling between vegetative and floral parts, resulting in strong intramodule correlations but weak correlations between modules[14]. Similarly, antagonistic interactions such as predation can impose strong correlational selection on behavioural traits, leading to tighter phenotypic integration and adaptive multivariate phenotypic plasticity in stickleback fish[15,16]. Studies of the outcomes of artificial selection and domestication processes have also revealed that correlations between animal personality traits have sometimes become decoupled, compared with the ancestors where these traits were more strongly genetically correlated[17].

In light of the genomic revolution, time is now ripe to evaluate the predictions[13,4] made about the evolution of genetic architecture and to ask: have they been confirmed or overturned by recent findings? In particular, are molecular signatures consistent with correlational selection having shaped the genomic architecture of organisms[6,18] and promoting functional integration, for example, through linkage or pleiotropy? Here, we review quantitative genetic theory and data on correlational selection and link these to the partly separate literature on modularity and evolvability, as well as to recent genomic research. Our aim is to synthesize insights from

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Box 1 | What is correlational selection?

Correlational selection involves several interrelated concepts. Here, we define the most important terms.

The individual fitness surface

Imagine a function relating an individual's trait values to that individual's expected lifetime fitness (Fig. 3). Supposing fitness depends on two traits, we can depict the fitness function as a three-dimensional surface. Horizontal axes represent trait values and elevation represents fitness. Fitness peaks and valleys represent regions in trait space with high and low fitness, respectively. Individual fitness surfaces can take almost any shape, including single-peaked surfaces, multi-peaked surfaces or ridges (Fig. 3), and can involve any number of traits.

A pioneering study[26] of colouration and behaviour in garter snakes provided one of the first empirical examples of how individual fitness surfaces illustrate correlational selection in a natural population (see figure). A snake's colour pattern could be either blotched or striped. Moreover, snakes either crawled in a straight line or reversed directions repeatedly when evading predators. Striped snakes had higher fitness when they fled predators in a straight line, whereas blotched snakes had higher fitness when they reversed directions. Therefore, survival depended on the interaction between two types of trait—colour and behaviour—rather than on single traits. Interestingly, colouration and behaviour were also genetically correlated with each other[128], providing empirical support for the prediction[4,13] that correlational selection can promote and maintain genetic correlations.

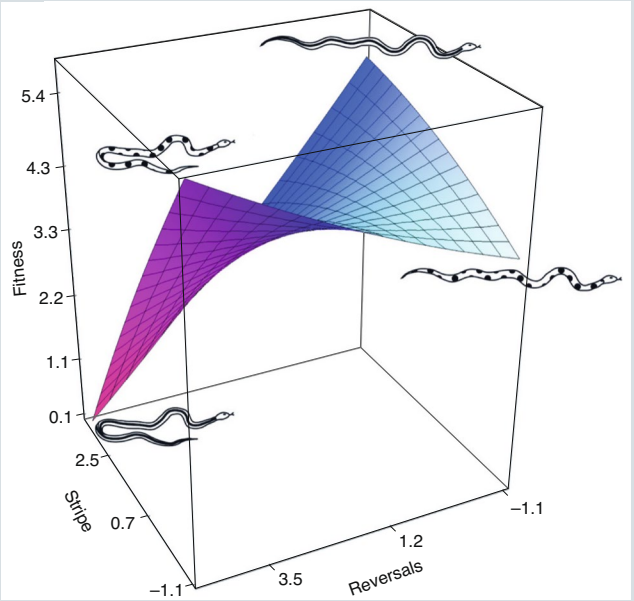

Figure adapted with permission from ref. [26], SSE/Edmund D. Brodie.

An operational definition of correlational selection

Correlational selection occurs when the relationship between an individual's trait value and expected fitness for one trait depends on that individual's trait values for other traits. Direct selection acts in such a way as to establish or maintain genetic and hence phenotypic correlations among traits[6]. One way to think about correlational selection is to imagine slicing the fitness surface parallel to one of the trait axes. If the slices differ in shape as we proceed along the fitness surface (Fig. 3a), then fitness is the result of interactions between traits.

A classic study[19] showed that correlational selection could be measured by using simple regression approaches. If we assume that traits have a multivariate normal distribution, then the fitness surface can be estimated by a regression of the form (in the bivariate case):

$$w(z_1, z_2) = \alpha + \beta_1 z_1 + \beta_2 z_2 + \frac{1}{2}\gamma_{11} z_1^2 + \frac{1}{2}\gamma_{22} z_2^2 + \gamma_{12} z_1 z_2 + \varepsilon,$$

where α is an intercept, z_1 and z_2 are trait values and ε is a residual term. The parameters β_1 and β_2 are the linear selection gradients, which estimate directional selection on each trait. The matrix of quadratic selection coefficients $\gamma = \begin{bmatrix} \gamma_{11} & \gamma_{12} \\ \gamma_{12} & \gamma_{22} \end{bmatrix}$ estimates stabilizing, disruptive and correlational selection. The diagonal elements of γ measure quadratic selection on each trait (that is, stabilizing or disruptive selection), whereas the off-diagonal elements represent correlational selection. Thus, non-zero off-diagonal elements of γ constitute evidence of correlational selection.

Fitness epistasis and epistatic selection

Much of the fitness variation in complex phenotypic traits originates from allelic variation at individual loci, each with small fitness effects. Favourable trait combinations at the organismal level often also reflect favourable allelic combinations at separate sets of loci. At the genomic level, correlational selection occurs when the fitness effects of a particular locus depend on the genotype at another locus or, more generally, depend on the genetic background. This situation is often described as fitness epistasis or epistatic selection, which can have a big impact on genome evolution[6,18].

these different fields and to point out new directions for future research at their intersections.

Quantification and visualization of correlational selection

The first quantitative treatment of correlational selection was provided in 1983[19] (Box 1). The pioneering authors introduced statistical tools to measure selection on continuously distributed phenotypic traits by estimating selection coefficients that could be incorporated into the equations for predicting evolutionary responses. Below we discuss the interpretations of those coefficients and review the methods to estimate them.

Individual fitness surfaces are often complex, but can be analysed to reveal the operation of correlational selection (see definition in Box 1). Correlational selection is especially likely when the fitness surface resembles a ridge that is not parallel to either trait axis (Fig. 3a), as this form of selection favours particular combinations of trait values over others and thereby selects for a non-zero correlation between traits (Box 1). Correlational selection can also arise alongside disruptive selection, for example, when the fitness surface resembles a valley that is not parallel with either trait axis (Box 1 and Fig. 3).

The measurement of correlational selection requires data on the fitness and trait values of multiple individuals (Fig. 3b). The major goals of such analyses are to visualize the fitness surface and estimate coefficients that describe it[5]. In empirical studies, the true surface is unknown, but we can deduce its properties by approximating the surface with simple functions. Quadratic surfaces are often used to estimate coefficients corresponding to linear selection (β) and

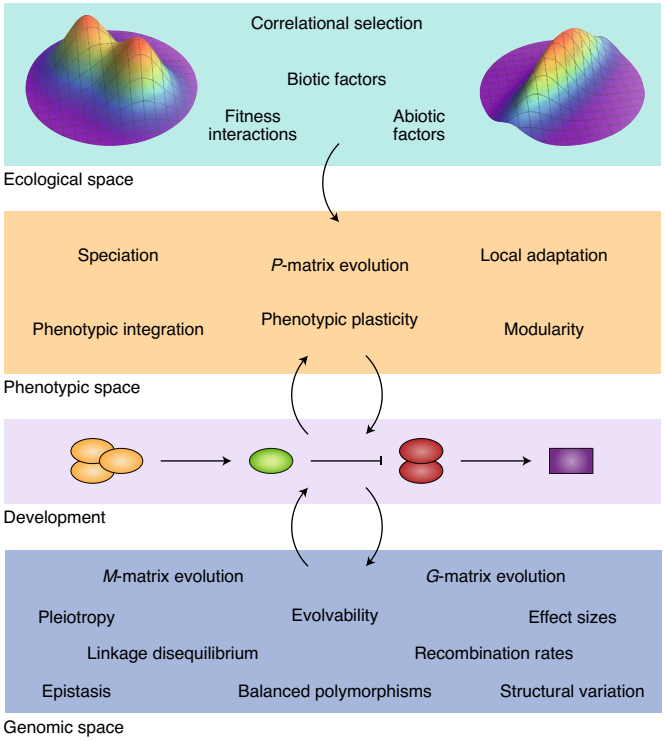

Fig. 1 | The scope of correlational selection and its links to different fields in evolutionary biology. Correlational selection is well understood statistically and theoretically (Box 1), but we still do not know the extent to which it has shaped genome evolution in diverse organisms. In a few cases, correlational selection has been studied and documented in natural field populations and in laboratory artificial experimental studies (Fig. 2). Correlational selection can strengthen or reinforce phenotypic and/or genetic correlations between traits[6,22,23,26], which may be governed by separate sets of loci, or break up non-adaptive or maladaptive genetic correlations, such as between the sexes[44]. These effects of correlational selection on phenotypic and genetic correlation structure have consequences for several populational level phenomena that are of interest in evolutionary genetics and developmental biology. These include *P*-matrix evolution, phenotypic plasticity, modularity, evolvability and phenotypic integration (upper part of figure). Correlational selection at the populational level can potentially drive the downstream evolution of genomic architecture and developmental pathways (coloured shapes in the purple box), which mediate the interrelations between the phenotypic and the genomic spaces[4,6,18] (lower part of figure). Correlational selection could preserve adaptive genetic correlations between traits that are governed by different sets of loci by suppressing recombination rates, thereby maintaining inversion polymorphisms and other structural genomic variation that is often associated with balanced genetic polymorphisms (Fig. 4). In addition, correlational selection could lead to adaptive pleiotropy, such as during range expansions when populations are far away from their adaptive peaks[123], and could shape patterns of epistasis between loci[12]. Finally, correlational selection can be involved in local adaptation, if different sets of character combinations are favoured in different abiotic[124] or biotic environments[27,28], but the consequences for speciation and other aspects of macroevolution remain largely unexplored. A single arrow represents one-way influence, whereas double arrows indicate two-way influences.

nonlinear selection (γ; Box 1)[19]. Unfortunately, it is difficult to visualize the fitness surface from the γ coefficients alone. However, the surface can be visualized by plotting it (Box 1) or by conducting a canonical analysis that estimates the principal components (eigenvectors) of the surface (Box 1)[5,7,8]. Despite their simplicity, quadratic coefficients can describe a wide variety of surfaces[5].

When a quadratic surface does a poor job of approximating the actual fitness surface, the surface can be visualized using non-parametric methods[20]. These techniques can reveal multiple peaks and valleys in the fitness surface (Fig. 3), if they exist, whereas the quadratic approaches will always depict a smooth and simple relationship, regardless of the ruggedness of the underlying fitness surface. However, non-parametric approaches have the shortcoming that they usually do not produce coefficients that are well-integrated into the equations of evolutionary change.

Our understanding of the empirical importance of correlational selection has lagged behind our understanding of the prevalence and consequences of directional selection[21], with only one meta-analysis of correlational selection published to date[22]. There are good reasons to expect correlational selection in a wide variety of ecological circumstances, and it might be particularly strong when fitness is affected by biotic interactions, which can generate strong and chronic selection on trait combinations[6]. Intraspecific interactions that have been shown to result in correlational selection often involve sexual or social selection[6]. Prime examples include selection on signalling traits such as colour[8,23,24], as well as selection on territorial behaviours, which can favour genetic coupling between traits such as aggression, dispersal and colonization ability[25] (Fig. 2). Interspecific interactions linked to correlational selection include predation based on colouration, morphology and behaviour traits[15,26], herbivory on plants[27], and mutualistic interactions between plants and their pollinators[28]. In many cases, the fitness surfaces are simple ridges or saddles, but sometimes the surface is more complex. Indeed, complex fitness surfaces could be common[20]. A priori we might expect to see multiple fitness peaks in organisms with discrete sympatric morphs[6,8,26], or between ecotypes[29] or newly formed species[30].

Correlational selection and evolution of genetic architecture

Correlational selection is central to our understanding of how genetic architecture evolves. It is also closely connected, albeit not identical, to the concept of fitness epistasis in evolutionary genetics[31] (Box 1). Importantly, although the single-generation effects of correlational selection on the genetic and phenotypic composition are readily understood, the transmission of these changes across generations is a complex theoretical and empirical issue.

To address how the effects of correlational selection are transmitted across generations, we must define two parameters. The first is the additive genetic variance–covariance matrix (G), summarizing additive genetic variance for a set of traits[9,10]. The diagonal elements of G are the additive genetic variances, and the off-diagonal elements are additive genetic covariances (Fig. 3c; see also Section 1 in the Supplementary information). Additive genetic variances and covariances describe patterns of trait inheritance, and depend on the frequency and effects of alleles. The additive genetic covariances are critical from a multivariate standpoint, because they describe the extent to which inheritance of different traits tends to be non-independent. In the bivariate case, G can be represented as an ellipse containing 95% of the genetic values of the individuals in a population[32] (Fig. 3c). If two traits are strongly genetically correlated, the ellipse will be eccentric and oriented such that it is not parallel to either trait axis. That is, genetic covariances between traits result in directions of multivariate trait space with high (major axis of the correlation) and low (minor axis of the correlation) genetic variance, even if genetic variance is high in all individual traits[33] (Fig. 3). Importantly, the long axis of the G matrix (g_{max}) represents a genetic line of least resistance[34], the direction in phenotypic space that harbours the most genetic variance and along which the population most easily evolves (see 'Consequences for genetic variation and plasticity').

Multivariate phenotypic effects of new mutations constitute a second set of key parameters, which are summarized in the mutational variance–covariance matrix (M)[11,12]. Theory often assumes that

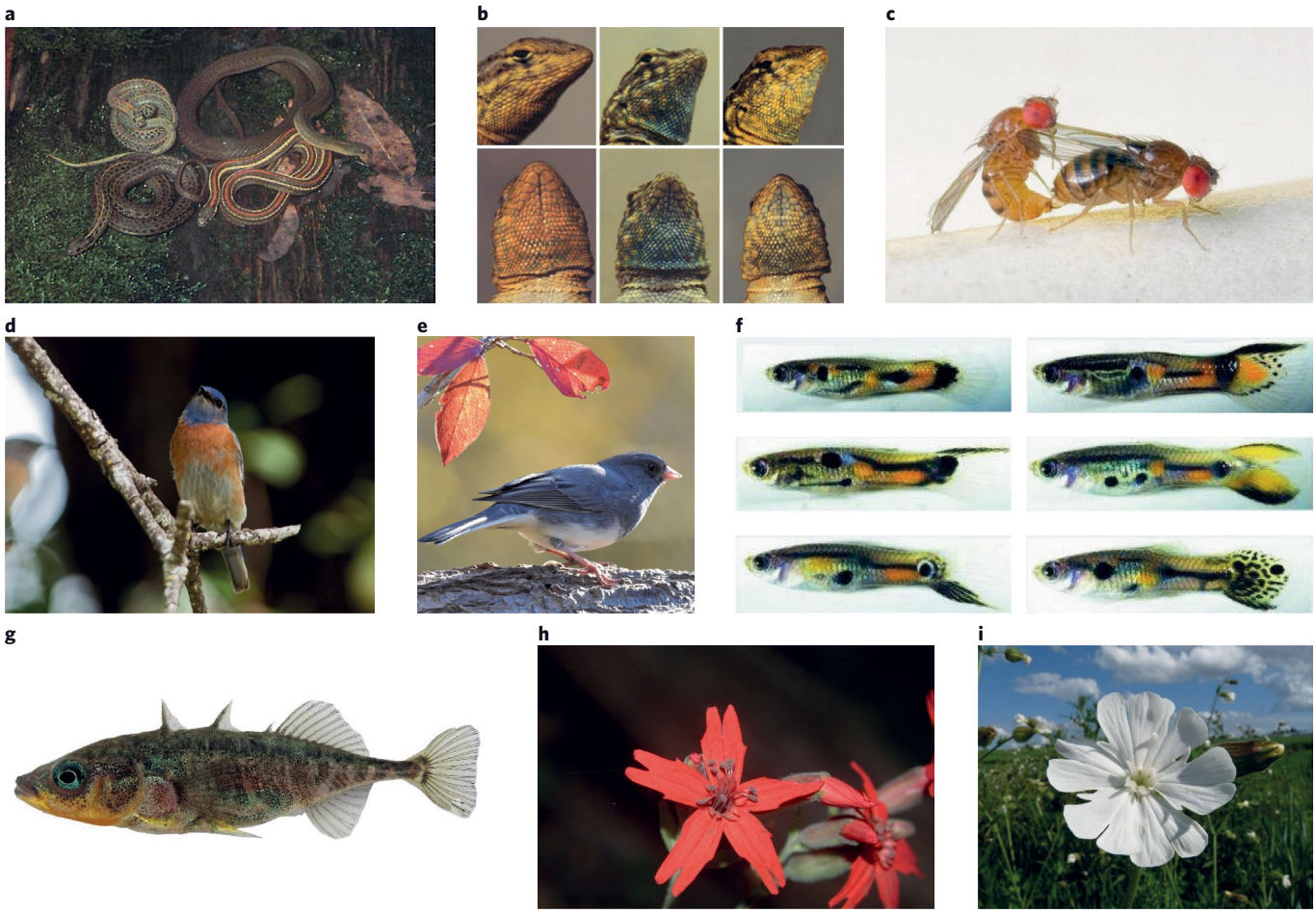

Fig. 2 | Phenotypic and quantitative genetics studies on organisms and traits in which correlational selection has experimentally been demonstrated or inferred, in the field or in laboratory studies. a, Northwestern garter snake (*Thamnophis ordinoides*). **b**, Side-blotched lizard (*Uta stansburiana*). **c**, Australian fruit fly (*Drosophila serrata*). **d**, Western bluebird (*Sialia mexicana*). **e**, Dark-eyed junco (*Junco hyemalis*). **f**, Guppy (*Poecilia reticulata*). **g**, Threespine stickleback (*Gasterosteus aculeatus*). **h**, Fire pink (*Silene virginica*). **i**, White campion (*Silene latifolia*). Correlational selection has been demonstrated and quantified for a number of different traits, including both discrete colour polymorphisms[6,8,23,26] (**a**, **b**, **f**) and continuous, quantitative characters[15,24,25,28,44,94] (**c**–**e**, **g**–**i**), both in animals and in plants. The ecological causes and selective agents driving such correlational selection have been shown to be predators (**a**, **g**), interspecific mutualists such as pollinators (**h**) and conspecific interactions, especially under sexual selection (**b**, **c**, **e**, **f**). In some of these studies, the phenotypic traits that were found or implicated to be under correlational selection were also genetically or phenotypically correlated with each other (**a**, **b**, **d**, **e**), suggesting that correlational selection can build up, promote or strengthen genetic integration between different traits. Conversely, artificial correlational selection has been demonstrated to be able to break up an intersexual genetic correlation in one study (**i**). Traits that can be subject to correlational selection include visual colouration traits (**a**, **b**, **e**, **f**), chemical communication traits (**c**), behavioural traits such as dispersal, aggression and personality (**d**, **g**) and structural traits such as size and shape (**h**). Credit: Edmund D. Brodie (**a**); **b** reproduced with permission from ref. [125], Springer Nature Limited; Antoine Morin (**c**); Erik I. Svensson (**d**); Ken Thomas (Wikimedia Commons) (**e**); **f** reproduced with permission from ref. [126], Springer Nature Limited; David Marques (**g**); Yuval Sapir (**h**); Adrien Favre (**i**).

mutational effects are normally distributed. In the univariate case, when a locus affects only one trait, this distribution can be described by a mean and a variance, and if mutations are unbiased, the mean will be zero. In the multivariate case, some loci might be pleiotropic[13], meaning that they affect more than one trait. In this case, the mutational effects are modelled as draws from a multivariate normal distribution. This distribution is described by mutational variances for each trait (diagonal elements of M) and mutational covariances between traits (off-diagonal elements of M). Positive mutational covariances mean that a mutation tends to affect both traits in the same direction, whereas negative mutational covariances indicate that mutations tend to affect traits in opposite directions.

Our analytical understanding of how correlational selection shapes the evolution of genetic variances and covariances comes from evolutionary quantitative genetic theory, particularly from the pioneering work in refs. [13,35,36], and ideas[2] about how selection on pleiotropic patterns could lead to parcelation or integration between traits. This pioneering work[13,35,36] suggested that inheritance should become aligned with the shape of the selection surface in well-adapted populations. Later, this model of selection on pleiotropic mutations was used to predict that genetic correlations should match functional interactions among traits[4]. Recently, this suggestion was extended to predict a three-way alignment among selection, inheritance and mutation[12].

How short-term responses to correlational selection are transmitted across generations depends on the distribution of allelic effects and the persistence of selection. Correlational selection can create genetic correlation by promoting linkage disequilibrium between alleles that affect two different traits[6]. However, such changes are expected to be eroded rapidly due to recombination if selection

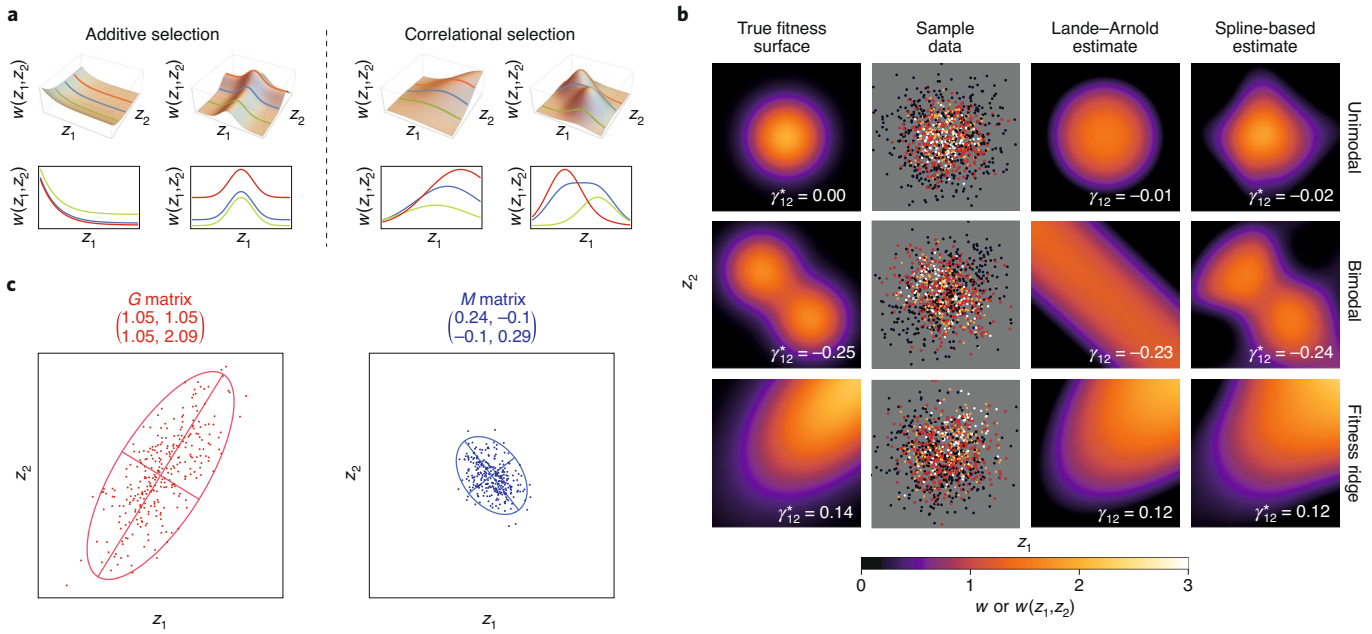

Fig. 3 | Illustration of correlational selection, with important parameters used to quantify it and determine how its effects are carried across generations. **a**, Example fitness surfaces for hypothetical traits z_1 and z_2 (top row) and conditional fitness curves for z_1 given fixed values of z_2 (coloured lines in both rows). When selection is additive, the fitness effects of z_1 are independent of the value of z_2. The conditional fitness curves are then identical apart from their height above the trait axes (bottom row, left of the dashed line). Under correlational selection, in contrast, the fitness effects of z_1 depend on z_2, and so the shape of the conditional fitness curves changes with the value of z_2 (bottom row, right of the dashed line). **b**, Estimation of multivariate fitness surfaces from samples of individual trait values, z_1 and z_2, and individual relative fitness, w. Expected relative fitness is $w(z_1,z_2)$. The true fitness surface (first column) is unobservable but can be sampled by measuring the relative fitness of individuals in a population (second column). The true surface can then be estimated via quadratic regression (third column) or by non-parametric smooth splines (fourth column). See Section 3 in the Supplementary information for full details. **c**, The *G* matrix (red, left) is the variance–covariance matrix of additive genetic effects (that is, breeding values) for a multivariate phenotype. The *M* matrix (blue, right) is the variance–covariance matrix of additive mutational effects. Points represent individual breeding values (red) and additive mutational effects (blue), respectively. If the distribution of point values is multivariate normal, it can be summarized via an ellipsoid. The principal axes of the ellipsoid (crossed lines) align with the eigenvectors and their lengths are proportional to the square roots of the eigenvalues. The major axis, associated with the largest eigenvalue, indicates the direction of maximum additive genetic or mutational variance.

is relaxed in subsequent generations[6], suggesting that changes in genetic architecture due to this kind of correlational selection may be transient[37] unless correlational selection is persistent[6]. More realistically, if correlational selection acts on traits whose expression is affected by alleles with pleiotropic effects, then correlational selection will alter the frequencies of those pleiotropic alleles. Therefore, the distribution of mutational effects has important consequences for the efficacy of selection on genetic covariances.

Two recent advances have increased our general understanding of the evolution of genetic architecture. First, increasingly powerful computer simulations have enabled researchers to explore the long-term effects of correlational selection and mutation on the evolution of genetic covariances[9–12], expanding our knowledge beyond the case of mutation–selection balance under the classical infinitesimal model[35,38]. Second, a rapid increase in genomic data has provided insights into the empirical distributions of allelic effects in real populations. Combining both approaches provides exciting opportunities to understand how selection and genetics jointly shape the evolution of trait variation (see 'Genomic architecture and multi-character evolution').

Simulation-based studies have verified the prediction[4,13] that selection will cause standing genetic variation to become aligned with the fitness surface[9]. For instance, if the fitness surface is ridge-shaped, then populations will tend to harbour more variation in the direction of phenotypic space aligned along the crest of the ridge, and less variation perpendicular to the ridge. However, other factors also influence the genetic architecture of traits: genetic drift can cause *G* to fluctuate over evolutionary time[9] and a moving optimum stretches *G* in the direction of the movement[10]. Migration also increases the genetic variance in the direction of phenotypic space pointing towards the mean of the migrant source population in an island–mainland model[39]. Recently, it has also been emphasized that the mutational variance is aligned with the direction of phenotypic plasticity[3,40], affecting both *G* and *M*. One interpretation of such alignment between plasticity and mutational variance is that developmental systems might respond similarly to environmental novelty as they do to genetic mutation[40]. Moreover, all else being equal, correlations in *M* should generate correlations in *G*, because standing genetic variation ultimately arises via mutation.

Interestingly, influences between the fitness surface, *G* and *M* can flow in both directions. While *M* can influence the shape of *G*, the fitness surface in turn can shape both *G* and *M*[11,12]. Thus, if the fitness surface is a ridge in phenotypic space (Fig. 3), selection will cause the long axis of *G* to align with the ridge. If such a selective regime is stable over evolutionary time, selection can cause alignment between the fitness surface, *M* and *G*[12,41,42]. Simulations show that evolution of the mutational distribution is especially plausible when different loci interact epistatically[12]. Recent progress in molecular biology, development and genomics suggests that such epistatic interactions are extremely common[43]. Epistasis can therefore permit the evolution of the mutational architecture because selection maintains variation at loci that have favourable interactions under the prevailing selection regime.

A growing number of studies suggest that *G* can or has evolved in response to correlational selection (Fig. 2). For instance, one

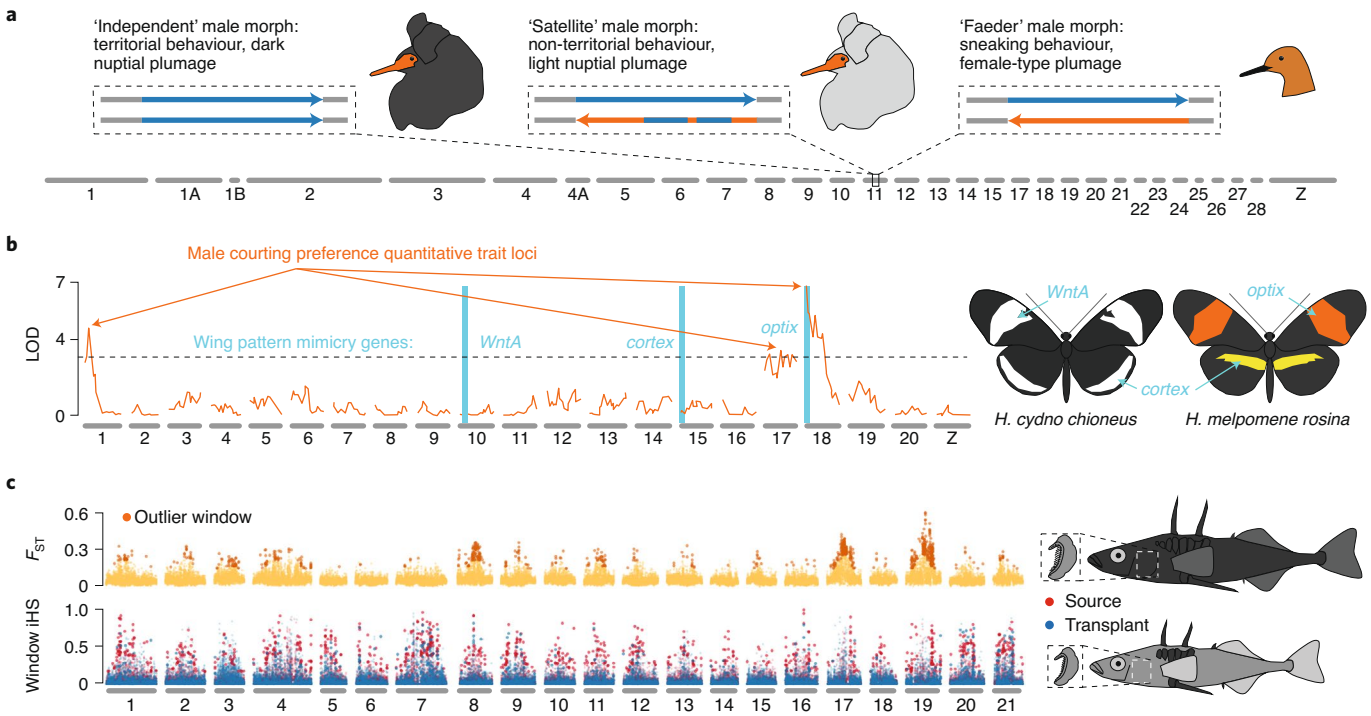

Fig. 4 | Examples of genomic trait architectures that might reflect past or ongoing correlational selection. We focus here on empirical examples where multiple loci are involved in the adaptive traits in question, as these reflect the most challenging situations to maintain adaptive genetic correlations between traits, due to the eroding effects of recombination when traits are governed by multiple unlinked loci. However, we underscore that correlational selection could equally well lead to the evolution of adaptive pleiotropy[123] as an alternative mechanism to maintain adaptive genetic correlations between traits. **a**, The complex mating polymorphism in male ruff (*Philomachus pugnax*) reproductive tactics involves multiple correlated morphological and behavioural traits. The different character combinations in the male morphs are preserved because of the lack of recombination between different loci that are held together in a single large chromosomal inversion[73,74]. Blue and orange arrows depict ancestral and inverted homologous chromosomal segements on chromosome 11. **b**, Assortative mating maintains linkage disequilibrium between unlinked colour pattern loci that are targets of correlational selection in *Heliconius* butterfly species. Linkage disequilibrium is facilitated by tight physical linkage between preference and trait loci on one chromosome[76]. Shown are logarithmic odds ratio (LOD) scores for male courting preference across the genome (orange) and the genomic position of three wing colour pattern genes (blue)[76]. **c**, In a multifarious selection experiment with threespine sticklebacks (*G. aculeatus*), the predicted phenotypic changes in multiple traits were caused by widespread underlying genomic changes that could potentially be attributed to correlational selection for different character combinations in the different phenotypes[127]. Shown are differentiation (F_{ST}) between source and transplant populations and the selection statistic integrated haplotype score (iHS)[127]. Grey bars in **a**–**c** represent the chromosomes of each species. Panel **a** adapted with permission from ref. [74], Springer Nature America, Inc.; panel **b** adapted with permission from ref. [76], PLoS; panel **c** adapted with permission from ref. [127], Springer Nature Limited.

study[44] imposed artificial correlational selection on combinations of male and female floral traits in the dioecious flower *Silene latifolia* (Fig. 2i) to test whether the between-sex genetic correlation was evolvable. High between-sex genetic correlations would potentially constrain the evolution of sexual dimorphism. Between-sex genetic correlations broke down after a few generations of selection[44], however, suggesting that these correlations are due to linkage disequilibrium, which is expected to break down rapidly under artificial correlational selection or recombination. But in another plant study, genetic correlations were remarkably stable across several generations, suggesting that pleiotropy caused these correlations[45].

Genomic architecture and multi-character evolution

The development of next-generation sequencing provides new opportunities to investigate correlational selection beyond what has been possible with classical quantitative genetics. Genomic data have allowed us to pinpoint the genetic basis and architecture of traits, to estimate empirical distributions of allelic effects in real populations, to reconstruct the evolution of genome architecture relevant for trait evolution and to detect correlational selection from molecular footprints (Box 2).

Recent studies using quantitative trait loci mapping, genome-wide association studies (GWAS) and whole genome sequencing of population samples (Box 2) have revealed that most genotype–phenotype maps[46] are complex. Most traits are determined by a large number of genes of small effect, consistent with the so-called 'polygenic model' of inheritance[38] allowing efficient quantitative genetics modelling, ignoring details of multilocus inheritance by assuming the infinitesimal model[47]. However, empirical effect size distributions are often exponentially distributed[48,49], with a few genes of major effect controlling a minority of traits for which the infinitesimal model is violated[50], and that often have an important role in adaptation and speciation[51,52]. Molecular studies have further revealed that many functional genetic variants are pleiotropic and affect multiple traits[53]. Multiple-mapping approaches, enabling joint estimation of effects on multiple traits, hold great promise to further improve our understanding of pleiotropy[54]. Molecular studies have also revealed that epistasis is common[55], with genotype–phenotype maps typically being highly nonlinear[56], suggesting pervasive epistasis in genotype networks[43]. The importance of epistasis is controversial because linear quantitative genetic models are rarely improved by the addition of

Box 2 | Methods to study genomic signatures of correlational selection

Genomics can inform quantitative genetics

Owing to the highly polygenic nature of most traits, quantitative genetics can succesfully predict short-term evolutionary change in phenotypes[58]. Genomic tools can, however, be integrated with quantitative genetics methodology to expand our understanding[38,58,82]. For example, the so-called Genomic Best Linear Unbiased Prediction (GBLUP) approach[82] allows the pedigree-relatedness matrix of an 'animal model' to be replaced by a marker-based relatedness matrix to infer genetic variances and covariances, that is, *G*. By accurately determining the proportion of genome shared, such genomic approaches may improve the estimates of *G* compared with using pedigree data alone, where relatedness is based on a shallow pedigree[129].

Genomic approaches can also provide information about mutation rates of single nucleotide polymorphisms and indel variants, thereby improving our understanding of the role of mutation rates in evolution[130] and the importance of mutational pleiotropy and *M*-matrix evolution[83–85]. Of particular interest are the effects of new mutations on genetic variances and covariances, that is, *M*[83–85]. A promising approach is the combination of mutation accumulation experiments with estimates of *M* and *G*[85–87]. Studies on mutation accumulation lines have revealed strong mutational pleiotropy across the transcriptome[85]. Such strong mutational pleiotropy in *M* contrasts with weaker pleiotropy in *G*, suggesting that correlational selection operates against maladaptive strong mutational covariance, resulting in a weakening of pleiotropy during the course of the life cycle[83,84].

To quantify outcomes of correlational selection, we need to identify the genetic loci under such selection. Traditionally, this has been achieved by quantitative trait loci mapping, admixture mapping and GWAS[131], which have limited power to detect small-effect-size genes. Newer approaches map pleiotropy by simultaneously associating genomic loci with multiple traits[54] and can also detect epistatic interactions using machine learning algorithms[132].

Detecting the genomic signatures of correlational selection

Correlational selection could potentially be inferred from signatures of selective sweeps at loci under strong selection[133] or, for highly polygenic traits, allele frequency shifts that are not explainable by genetic drift[90,134]. Selection on polygenic traits often leads to small frequency changes in many genes, which are more difficult to detect[134]. As correlational selection favours certain allele combinations, one outcome is deviations from the Hardy–Weinberg equilibrium. The build-up of linkage disequilibrium between alleles at unlinked loci should in principle be detectable both across individuals and between age classes within populations. Genomic data may also indicate whether recombination suppression leading to trait correlations[67], such as in supergenes or genomic rearrangements, has been favoured by correlational selection. On longer timescales, genomic data can reveal how such supergenes are gradually built up and assembled via gene duplications and neofunctionalization[75]. Experimental assays such as introgression lines[135] or reciprocal crosses of diverged lineages[136] can be used to confirm whether combinations of alleles or genomic regions are under correlational selection. Evolve and resequence experiments comparing populations before and after selection[137], or studies of allele frequency time series during an experiment[138], can give insights into allelic interactions and genomic and phenotypic responses to experimentally imposed selection[62,127].

Bridging the genotype–phenotype–fitness map

Ideally, the genotypic and phenotypic levels should be quantified alongside the adaptive landscape[108,139] and integrated into a genotype–phenotype–fitness map. This integration has been achieved for very few non-model organisms such as threespined sticklebacks[29], Bahama pupfish[30] and *Timema* stick insects[59], for which the fitness landscape was mapped experimentally with information about the genomic architecture of traits. Experimental field studies on fitness epistasis combined with genomic data is a promising integrative approach to detect the genomic consequences of correlational selection[59].

interaction terms[57]. However, genomic quantitative genetic studies that incorporate a more precise estimate of the shared proportion of the genome have revealed that higher-order variance components are not negligible[58]. Interestingly, a recent study of *Timema* stick insects has shown that correlational selection arose from fitness epistasis due to ecological factors (predation), in spite of the underlying traits (colour) having an additive genetic basis[59].

These insights about the genetic architecture of traits have implications for the evolutionary response to correlational selection. One emerging insight from experimental evolution studies is that evolutionary changes in traits can often be achieved via many alternative 'genomic solutions', suggesting important roles for redundancy and historical contingency in evolution[60]. Further, parallel evolution is often frequent for fitness itself, but less common for phenotypes, and less common still at the levels of genes or individual mutations[61]. For example, one study[62] sequenced genomes of Atlantic silverside fish (*Menidia menidia*) selected for small and large size. Despite highly parallel phenotypic changes and several parallel allele frequency shifts in growth-related genes, genomic adaptation in one line was contingent on the presence of a large inversion with moderate phenotypic effect[62]. On the other hand, pleiotropy, functional constraints and the presence of major-effect loci may limit the number of redundant genomic solutions in response to correlational selection[63]. For example, threespine sticklebacks adapting to freshwater habitats show highly repeatable evolution at a pleiotropic major-effect locus[64,65].

Correlational selection changes the genetic covariances among traits and thereby ultimately shapes the evolution of genome architecture. Although many different mechanisms underlie genetic covariances[66], the two basic causes are linkage disequilibrium and pleiotropy[38]. Linkage disequilibrium captured by physical linkage is one genomic cause of trait correlations, in which recombination is suppressed in heterochromatic regions, in genomic rearrangements, on sex chromosomes or due to a high density of transposable elements[67]. For example, a study[68] that sequenced 304 *Arabis alpina* genomes found that the *S* locus supergene responsible for strict outcrossing was in a linkage disequilibrium block that included high levels of polymorphic transposable elements. Genomic rearrangements such as gene duplications, translocations, chromosomal fusions or inversions can also maintain linkage disequilibrium, due to disrupted meiotic chromosome pairing reducing recombination or the joint forces of physical linkage and selection[69–71]. Linkage disequilibrium may be preserved in deep evolutionary time, forming so-called 'supergenes', some of which might resemble sex chromosomes[69,72–74] (Fig. 4a). There are several empirical examples of how co-selected complex trait combinations, bound to supergenes, cause behavioural and morphological differences between discrete morphs with different reproductive tactics (Fig. 4b)[72–74]. For example, a recent study in the heterostylic plant genus *Primula* revealed the build-up of an *S* locus supergene controlling style, anther and pollen grains via gene duplications and neofunctionalization[75].

Even in the absence of physical recombination suppression, genetic covariances among traits can arise through linkage disequilibrium between loci[6]. Such linkage disequilibrium can potentially be maintained by assortative mating among individuals with the same correlated trait combinations[76] and by strong divergent or disruptive selection favouring several correlated trait optima within[6,77] or between populations[78]. Correlational selection can also theoretically lead to speciation through reinforcement of assortative mating by the evolution of genomic coupling between preference and trait loci, even if they are initially unlinked[6,76,79]. There are several examples of ecotype or species pairs where inter-chromosomal linkage disequilibrium is maintained either by strong selection[80] or a combination of strong selection and assortative mating[81], with some studies demonstrating genomic coupling between unlinked preference and sexually selected trait loci[76].

Genomic tools in combination with quantitative genetic approaches also enable us to obtain better estimates of G (Box 2)[58,82]. In addition, comparisons between the genetic variances and covariances of M and G can reveal the presence of correlational selection and how it operates during the organismal life cycle, and shapes both mutational pleiotropy and pleiotropy of the standing genetic variation[83–85] (Box 2). Mutation accumulation experiments have revealed strong mutational pleiotropy[85–87] and have indicated that correlational selection on such pleiotropy leads to a reduction in the corresponding genetic correlations in G[83] (Box 2). Thus, correlational selection might operate against mutational pleiotropy, resulting in a discrepancy between M and G. Consequently, spontaneous and positive mutational correlations among traits could largely be maladaptive and reflect the input from mutation–selection balance[86]. This contrived example underscores the point that correlational selection can not only strengthen adaptive genetic correlations among traits, it can also weaken and break up maladaptive genetic correlations[44,83].

Finally, genomic information from several populations can be used to address how multiple traits co-evolve, using information from a co-ancestry matrix, which can be estimated with a handful of marker loci[88]. A recent study[89] used such an approach and found evidence for correlated character evolution in the timing and growth rate across 16 silver fir (*Abies alba*) populations. While this methodology is limited to describing the average effect across all causal loci, such approaches could enable us to describe the genomic architecture of trait correlations in terms of individual loci, their physical distribution across the genome and their effect sizes[90].

Consequences for genetic variation and plasticity

The intuition that pleiotropy slows and constrains evolution was well articulated in a previous study[91], which updated Fisher's classical geometric model[92] to show that phenotypic complexity slows adaptation when pleiotropy is universal. However, this link between pleiotropy and constraints on evolvability—the ability of a population to respond to selection[93,94]—has recently been challenged. First, pleiotropy may be largely confined within functional, integrated trait modules[46], allowing traits in separate modules to adapt semi-independently[2]. That is, as predicted in ref. [4], correlational selection will select for congruent phenotypic covariances[13]. Moreover, individual-based simulations with divergent multivariate directional selection, pushing groups of traits in opposite directions, have shown that phenotypic variation can indeed evolve to become more modular[95]. Increased modularity may also evolve when environmental fluctuations favour new combinations of conserved functions[96] or when selection across multiple environments favours the expression of partially overlapping sets of genes[97]. While these studies suggest that circumstances favouring high evolvability can drive the evolution of modularity, theory has also shown that highly integrated and pleiotropic genetic architectures can have high evolvability[93]. There is still considerable room for development of theory to predict when we expect modularity to emerge as a solution to adaptive challenges (Section 2 in the Supplementary information).

A common feature for the evolutionary origin of modularity is directional selection, although modularity can also evolve as a consequence of selection for robustness to environmental perturbations[98], and merely adding selection to models with universal pleiotropy does not produce stable variational modules[99]. The responsiveness of modularity to directional selection also limits its use as a predictor of long-term evolutionary responses, perhaps explaining why functional modularity is only a modest predictor of co-evolutionary rates of evolution among genes[100]. Another potential explanation for this pattern is that functional and variational modularity only partially overlap. Empirical evidence of co-expression of genes is strong[101], but the question of whether these co-adapted gene modules are organized as variational modules is controversial. Some studies using transcriptional data showed that genetically correlated transcripts tend to share developmental pathways, reflecting transcriptional modules that are mostly enriched with functionally related genes[102,103], whereas other studies could not find substantial overlap between gene expression and functional groupings[104]. Modular functional capacities do not require structural modularity[105], and modularity at the level of gene regulation may better predict evolvability[106]. The mismatch between variational modules and functional gene groupings can complicate the semi-independent evolution of phenotypic modularity.

Multivariate perspectives show that additive genetic variation within populations is distributed very unevenly across traits, with some linear combinations of traits accounting for most of the variance (that is, g_{max}), while other trait combinations are associated with very little variance[33]. This pattern can stem from genetic variation being funnelled through a few central developmental pathways, mediated by few developmental genes of large effect[107]. There has been considerable interest in g_{max} (see 'Correlational selection and evolution of genetic architecture') because it can either facilitate or bias evolutionary responses to selection depending on its alignment to the selective surface[108]. Additive genetic variance is determined by the effects and frequencies of contributing alleles, and at the genomic level, the initial response to selection should be dominated by loci with relatively high intralocus variance and large effect. Although genomic studies, such as GWAS, have a tendency to detect loci with high frequencies of minor alleles and larger effects[109], empirical evidence of the contribution of variants to additive genetic variance points to mostly rare variants with mainly small but highly pleiotropic effects[110]. If g_{max} reflects the most common empirical pattern, selection aligned with g_{max} should promote adaptation through minor allele frequency changes at many loci[111].

The mere presence of additive genetic variation is not sufficient to predict evolutionary outcomes, as the response to selection depends on the orientation of selection relative to the distribution of genetic variation[94,112]. Only a few studies have measured both multivariate linear and quadratic selection and the distribution of genetic variation for those phenotypes. These studies typically demonstrate relatively low genetic variance in the multivariate trait combinations associated with fitness variation, which slows down phenotypic evolution[113]. However, the causes of low genetic variance for multivariate phenotypes currently under selection, and thus the longer-term consequences of the covariance patterns, remain poorly resolved[33].

As there is substantial genetic variance in other directions of trait space besides g_{max}, changes in the orientation of selection could result in relatively unbiased, rapid adaptation[94]. Moreover, pleiotropy can be context-dependent[101,114], meaning that apparent pleiotropic constraints may shift in novel environments or evolve through epistatic interactions. For instance, changes in the selective environment could remove bias by changing the orientation of genetic variation[40], potentially through context-dependent pleiotropic effects of alleles[114], or through rapid evolution of G, which might

be particularly likely if trait covariances are generated through opposing pleiotropic effects across contributing loci[93]. For example, a recent experimental study in yeast demonstrated that while alleles had pleiotropic effects on two life-history traits, variation in effects across environments resulted in genetic correlations ranging from −0.5 to 0.5[115]. Finally, mutational pleiotropy is only one of several factors influencing standing genetic variation, which also depends on multivariate selection and linkage disequilibrium.

The relationship between how genetic variance changes across contexts and how phenotypes respond to the environment directly (that is, phenotypic plasticity) can determine the longer-term outcomes of correlational selection. A recent meta-analysis of published estimates of *G* and plastic responses to novel environments suggested that multivariate phenotypic plasticity might correspond to axes of genetic variation associated with substantial standing genetic variation[40]. This study and theory[3] suggest that bias in evolutionary response generated through *G* can become recapitulated through phenotypic plasticity. Clearly, more work is needed to understand how environmental and genetic information are interpreted through the developmental systems (Section 2 in the Supplementary information).

Conclusions

Here, we have re-visited early suggestions[4,13] that correlational selection can shape genetic and phenotypic architecture in light of the recent genomic revolution. These early insights are consistent with increasing empirical evidence of genomic coupling and recombination suppression that could have arisen by correlational selection, although direct evidence for this process, in most cases, is lacking. A remaining challenge is therefore to integrate organismal level research on correlational selection on phenotypes with genomics and developmental biology. Below, we point to some promising new avenues for future integrative research in this exciting area.

First, despite empirical evidence that correlational selection can build up or eliminate genetic correlations between co-selected traits (Fig. 2), our knowledge of the mechanistic (that is, genomic and developmental) underpinnings of such changes is still limited. To what extent are such changes caused by transient changes in linkage disequilibrium or the evolution of adaptive pleiotropy, and what is the relationship between modularity and correlational selection? We are only just beginning to understand the genomic mechanisms involved in adaptive recombination suppression caused by correlational selection, including the roles of supergenes[69,71], structural genomic rearrangements[70] such as gene duplications, chromosomal fusions or inversions and other mechanisms including transposable elements[67,68]. Promising future research directions in the study of the genomic consequences of correlational selection include the use of genomic tools to study how correlational selection might lead to the gradual build-up of supergenes[75] and how such selection might operate on mutational pleiotropy across the organismal life cycle, using a combination of mutation accumulation experiments, quantitative genetics and quantification of gene expression changes during ontogeny[83,85–87].

Second, the relationship between phenotypic plasticity and correlational selection is largely unknown. The traditional perspective has been that correlational selection would primarily shape genetic correlation structure, by either strengthening or weakening genetic correlations between traits[4,6,44]. Research on stickleback fish has found that predation results in changed phenotypic correlation structures[15], but some of these phenotypic changes might reflect multivariate phenotypic plasticity rather than changes in genetic integration[16]. How genetic covariances and multivariate phenotypic plasticity jointly evolve under correlational selection is therefore a largely unexplored research area with great potential[16,40]. More generally, as correlational selection in the past might have shaped either phenotypic or genetic correlations (or both), it leaves an evolutionary 'memory' of past selective environments[116] that can reveal itself in the form of alignment between the selective surface, the phenotypic variance covariance matrix *P*, *G* and *M*[12,41,42].

Third, the importance of correlational selection in speciation and macroevolution is largely unknown, despite early work on evolutionary allometry and the idea of evolution along 'lines of least resistance'[34,117]. Recent research on shape–size allometry[118], brain–body size allometry[119] and metabolic allometry[120] has revealed that allometric relationships are not static evolutionary constraints, but can be altered by selection. Specifically, correlational selection could maintain adaptive allometric slopes, either due to internal causes related to deleterious pleiotropy[118], or because external ecological factors make certain slopes more beneficial than others[119,120].

Finally, we also see a great potential for research on the genomic consequences of correlational selection in the fields of animal and plant domestication[17], and in the context of dispersal strategies, social behaviours and personalities[16,25,121]. Humans might have consciously or unconsciously either eliminated or strengthened genetic correlations between traits during domestication of plants and animals through artificial correlational selection on suites of traits, which in some cases has led to adaptive introgression back into wild relatives[122]. One result of domestication is the formation of suites of co-inherited traits with distinct genomic signatures[17]. In natural populations, co-adaptation between social behaviours and dispersal[121] could frequently have been driven by correlational selection, resulting in increased genetic integration[25]. Artificial correlational selection to either strengthen[118] or eliminate genetic correlations[44] is a promising experimental approach in this context.

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Author contributions

E.I.S. and A.R. conceived the paper, organized the writing and put together the first draft, based on input and written material from the other authors. All authors contributed to written sections, figures, Supplementary information, and improving and finalizing the manuscript. All authors approved the final manuscript version prior to submission and after acceptance.

Competing interests

The authors declare no competing interests.

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