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Evolutionary consequences of cryptic genetic variation

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Phenotypic evolution depends on heritable variation in phenotypes. A central aim of evolutionary biology, therefore, is to understand how processes generating phenotypic variation interact with selection and drift to result in phenotypic evolution. Recent studies have highlighted the propensity for populations to harbor genetic variation that contributes to phenotypic variation only after some environmental or genetic change. Many authors have suggested that release of this cryptic genetic variation by stressful or novel environments can facilitate phenotypic adaptation. However, there is little empirical evidence that stressful or novel environments release cryptic genetic variation, or that, once released, it contributes to phenotypic evolution. We argue that empirical studies are needed to answer these questions, and identify the empirical approaches needed to study the relationship between environment, released cryptic genetic variation and phenotypic evolution.

Robustness, cryptic genetic variation and evolvability

The origin and maintenance of phenotypic variation is a central theme in evolutionary biology, because adaptive phenotypic evolution depends on heritable variation in phenotypes. Therefore, it is important to understand how genotypic variation translates to phenotypic variation and how this genotype–phenotype map is influenced by genetic and environmental changes. One of the more intriguing general observations in biology is that phenotypes are robust (see [Glossary](#)) to much environmental and genetic variation [1–4]. That is, individuals with different genotypes have the same phenotype, and the same phenotype is expressed despite variation in the environment. Robustness presents a conundrum to evolutionary biologists [1,3]: how can the constraint on phenotypic evolution implied by the limitation of phenotypic variation by robustness be reconciled with the remarkable phenotypic diversity of organisms?

A key consequence of robustness is the buildup of cryptic nucleotide variation, that is, variation that exists in the genome but is not expressed in the phenotype [1–3]. Cryptic genetic variation has been proposed as a general explanation of macro-evolutionary patterns such as saltatory evolution and major evolutionary transitions [2,3,5–7]. By preventing it from being expressed in the phenotype, robustness protects cryptic genetic variation from selection. Thus, genetic variation arises through mutation and

is retained or lost owing to random genetic drift. Drift (and recombination) can result in retention of varied combinations of mutations, both within and among loci. Cryptic genetic variation could therefore contain information for changes in trait values beyond that typically seen in the population, and for novel trait combinations [1,2,8].

Waddington [5] was among the first researchers to articulate a link between environmental stress and evolvability, the ability of a population to respond to selection [6,7,9–11]. Stressful or novel environments are predicted to overcome robustness, releasing cryptic genetic variation. In this way, heritable phenotypic variation becomes available only when populations need to adapt to new

Glossary

Adaptive optimum: the phenotype with the greatest fitness.

Additive genetic variance: genetic variance associated with the average additive effects of substituting one allele for another. In sexual populations, parents transmit genes rather than genotypes to offspring, and it is the additive component of genetic variance, therefore, that determines resemblance among relatives.

Autonomy: the fraction of genetic variation that is independent of other traits. Autonomous genetic variation is therefore the genetic variation that is unique for the trait of interest, excluding variation due to pleiotropic alleles [30].

Buffering mechanisms: any process by which robustness of phenotype is achieved.

Cryptic genetic variation: standing genetic variation that does not contribute to the range of phenotypes observed in a population under standard conditions, but that is available to modify a phenotype following changes in the environmental or genetic context.

Evolvability: the ability of a population to respond to natural or artificial selection. Response to selection depends on variation among members of the population in their phenotype, and the intergenerational transmission of that phenotypic variation. Therefore, a population's evolvability is inferred from information on the distribution of phenotypes and additive genetic variance.

Fitness: the contribution of offspring by any individual to the next generation. Many traits will contribute to fitness, affecting viability or fecundity.

Heritability: the ratio of additive genetic variance to total phenotypic variance, that is, the fraction of variation between individuals in a population that is due to their genotypes. Heritability is often used as a metric of evolvability.

Phenotypic variance: the dispersion of phenotypes about the population mean phenotype. The phenotypic variance–covariance matrix determines the opportunity for multivariate selection.

Pleiotropy: the effect of a single locus on multiple phenotypic traits. Pleiotropy is the property of alleles at a locus, which can vary in the number of traits they affect and the specific effects on each trait. The additive genetic covariances summarize the pleiotropic effects of all alleles in the population.

Robustness: the invariance of phenotypes in the face of genetic or environmental perturbation. Robustness is inferred when a genetic or environmental change results in greater phenotypic variance than observed for the wild-type genotype developing under common environmental conditions. Canalization is a particular type of robustness, which evolved owing to stabilizing selection about an optimal phenotype.

Visible genetic variation: standing genetic variation that contributes to phenotypic differences in the population and is therefore visible to selection in the current environment.

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conditions. This evolutionary scenario has increased in popularity following the identification of a plausible mechanistic link between robustness and environmental stress, the 90 kDa heat shock protein Hsp90 [6].

The hypothesized evolutionary significance of the release of cryptic genetic variation rests on several assumptions for which we suggest empirical support is weak: (i) that environment affects evolvability; (ii) that evolution based on visible genetic variation cannot account for macro-evolutionary patterns; and (iii) that recombination and drift operating on cryptic (neutral) mutations will generate novel phenotypes that are not possible under selection. Here we present evidence addressing these three points, and consider what further research is required to determine how cryptic genetic variation contributes to phenotypic evolution.

Does evolvability depend on environment?

Waddington and colleagues articulated the link between stress and evolvability as early as the 1940s [9], but the idea was largely neglected for decades. In 1991, Hoffmann and Parsons reviewed available data, primarily from life-history traits in *Drosophila*, and determined that heritability was typically higher under stress [12]. However, subsequent reviews of studies in other traits and taxa refute this conclusion in two ways [13,14]. First, evidence that environment has any effect on evolvability is weak. Few studies (15 of the 74 total reviewed by Refs [13,14]) statistically supported an effect of environment on heritability. Second, the trend was for lower, not higher, heritability under stress [14]. Empirical evidence therefore suggests environmental stress does not typically release cryptic genetic variation. However, we are cautious about drawing this conclusion, suggesting that pervasive experimental design problems leave unresolved the question of how environments affect evolvability of which traits to what extent. Here we consider three aspects of experimental design that will affect conclusions about the effect of environment on evolvability: environment, trait and evolvability metric.

Environment

Organisms exist within the context of a complex environment. A weakness of many studies relating evolvability to environment has been that manipulations involve only two levels (e.g. stressful versus non-stressful) of a single facet of environmental variation (e.g. temperature). There are several problems with two-treatment designs. First, environments can be difficult to categorize *a priori* (Box 1). This problem makes null results particularly difficult to interpret, as they might indicate robustness was not overcome or cryptic genetic variation was not released. Second, release of cryptic genetic variation is often considered an all-or-none response, but there is little data on the shape of the distribution of genetic variation across environments [7]. Different cryptic alleles might become expressed in response to different types or different levels of stressors [3]. Assaying evolvability across multiple environments is necessary for development of general insights into the relationship between environment and the release of cryptic genetic variation (Box 1) [7,11,14].

The complex, multifarious nature of the environment makes it difficult to artificially generate biologically

relevant variation. Nonetheless, the capacity to manipulate environments in the laboratory provides a powerful approach for identifying causal relationships; do changes in environment cause changes in evolvability? It is important, however, that laboratory studies focus on ecologically plausible environments, both in terms of the type and range of the stressors. Environmental variation experienced by natural populations is implicitly biologically relevant, but limitations on characterizing and replicating environments in the wild make it difficult to infer causality [15,16]. Such field research is, however, necessary to characterize the environmental variation experienced by wild populations and the temporal stability of environments. That is, are the levels of environmental variation demonstrated in the laboratory to release cryptic genetic variation common or rare in the wild, and are they transient or persistent?

Traits

Traits typically differ in their response to a particular environment [2,14,17]. Again, variation in either trait robustness or cryptic genetic variation might account for discrepancies in empirical results [14]. Robustness has been predicted to be greatest for traits under strongest selection, leading to the expectation that life-history traits (e.g. fecundity, longevity), which are expected to contribute most to fitness, will be less responsive to environmental manipulations than other (e.g. morphological) traits [18] (but see Ref. [1]). There is empirical support for this prediction [14,18]. Life-history traits are also thought to have a larger mutational target size (i.e. be influenced by more loci) than morphological traits, consistent with having more visible (and cryptic) genetic variation [19,20]. This suggests that more extreme stressors will be necessary to overcome life-history robustness, but that once robustness is overcome, life-history traits will exhibit the greatest change in evolvability. Further data are required to determine how relationships between traits and fitness, as well as trait genetic architecture (particularly the number of contributing loci), affect the release of cryptic genetic variation.

A further aspect of trait architecture that might affect release of cryptic genetic variation is whether traits are continuously or discretely distributed. Classic studies of cryptic genetic variation considered discrete traits (e.g. bristle numbers) [9]. Storage (and release) of cryptic genetic variation for such traits is understood using threshold models [2,6,10,21], whereby continuous genetic variation is translated into discrete phenotypic classes. When the underlying genetic variation is below the threshold, an individual has one form of phenotypic expression (e.g. four bristles) and above the threshold an alternative form (e.g. five bristles). Certain genetic or environmental changes can shift the threshold, changing the frequency of phenotype classes in the population.

Although continuously distributed phenotypes can also be studied using threshold models, such traits have received less theoretical or empirical attention [2]. Recent studies of Hsp90 have demonstrated release of cryptic genetic variation for discrete, but not necessarily for continuous, traits [6,17,22,23]. These studies suggest

Box 1. Classifying environments

In the wild, organisms experience a continuum of environmental conditions. Stressful and novel environments have been predicted to release cryptic genetic variation [5–7,10,11], but objective classification of environments poses a challenge. Defining environments by their effect on fitness can resolve this dilemma. Stressful environments (whether biotic or abiotic) are those that cause a decline in fitness [10]. Put another way, the adaptive optimum in stressful environments differs from that in the common environment such that populations are no longer locally adapted, resulting in a switch from stabilizing selection (about an adaptive optimum) to directional selection (toward a different adaptive optimum) (Figure I) [7]. Similarly, novelty implies naivete and a lack of local adaptation. Environmental stress and novelty can then be considered on a continuous scale: the greater the shift in adaptive optimum, the greater the level of stress or novelty.

There is some empirical evidence that novelty has a greater effect on evolvability than does stress [14], although whether this is because the adaptive optimum shifted further in environments experimentally classified as novel versus stressful is unclear [7]. Similarly, the greater effect on evolvability of laboratory manipulations versus naturally occurring stressors [14] might reflect a greater shift in adaptive optimum, but this remains to be determined. In general, we need to assay evolvability across a range of environments [7,11,14], and to determine selection acting on the population in each environment to characterize the relationship between environment, selection and evolvability (Figure II). Although empirical techniques are available for estimating selection [28,35,44], these have not yet been applied to the question of how evolvability changes with environment.

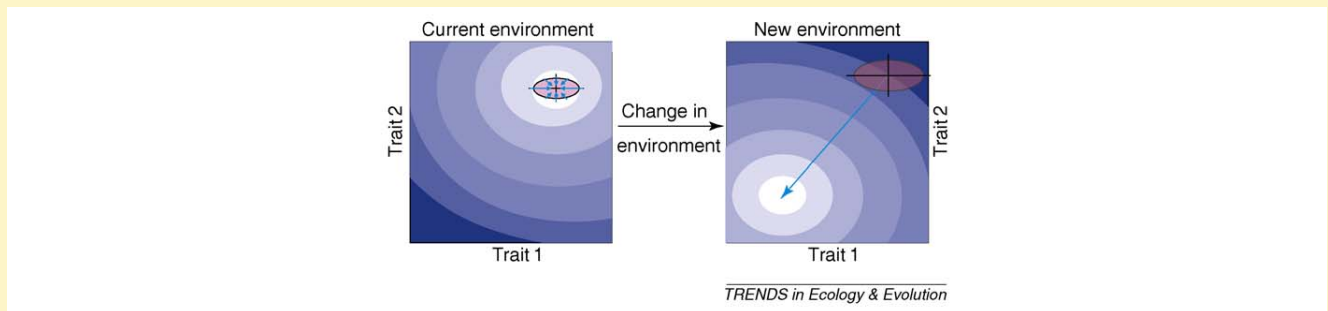


Figure I. Schematic of how selection and the expression of cryptic genetic variation differ among environments. The schematic is based on the adaptive landscape [44] for two traits. Fitness increases from dark to light (optimal phenotype shown in white), and rings of the same shade indicate regions of equal fitness. The direction of selection is shown by the blue arrows, stabilizing in the current environment and directional in the new environment. The pink ellipse summarizes the distribution of phenotypes in each environment, with the population mean phenotype indicated by the intersection of the ellipse axes. In the current environment, the population is locally adapted, experiencing stabilizing selection about the optimal phenotype (high values of both traits). In a new environment, the adaptive optimum shifts, and the population now experiences directional selection toward this new optimum (low values of both traits). The larger ellipse in the new environment indicates the change in environment has released cryptic genetic variation.

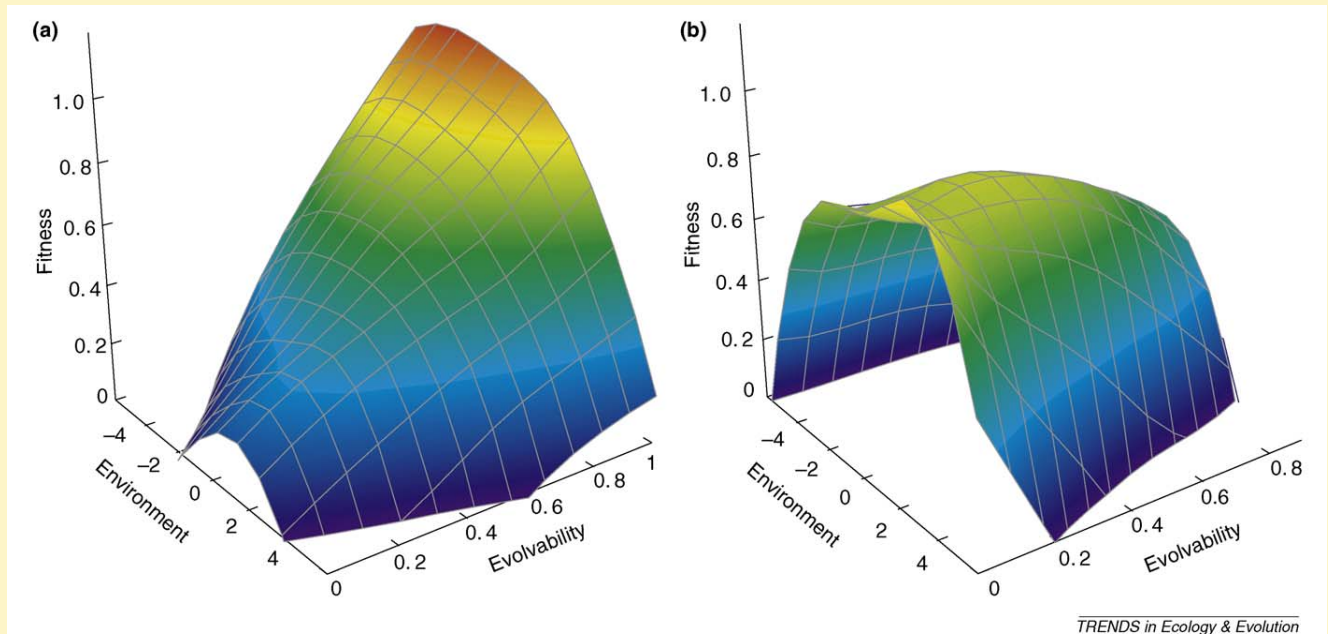


Figure II. Hypothetical relationships between environment, fitness and evolvability. Both graphs are centered on the current environment (zero), and fitness is highest in this environment. The height of the surface is indicated by color from cool to warm (highest points red, lowest points blue). (a) Evolvability is highest when fitness is highest (in the current environment) (e.g. [14]). (b) Evolvability is lowest when fitness is highest (current environment) (e.g. [12]).

differences in release of cryptic genetic variation for discrete versus continuous traits, at least in *Drosophila*. Manipulation of Hsp90 in *Arabidopsis* and in *Danio* released cryptic genetic variation for continuous traits,

but the effect was highly dependent on genetic background [17,24,25]. The inconsistency of these observations highlights our lack of understanding of how environment affects the expression of visible versus cryptic

genetic variation for continuously varying traits, such as life-history traits, which are likely to contribute strongly to fitness. Furthermore, we need to move beyond model organisms (e.g. *Drosophila melanogaster*) to detect generalities in trait relationships between environment and evolvability [2,23].

Evolvability metrics

Phenotypic evolution occurs at the level of the population, and depends on heritable phenotypic variation among members of the population. Informative evolvability metrics therefore need to capture this population-level variation in heritable phenotypes, providing a direct link to evolutionary theory. Heritability is the most commonly reported evolvability metric, and although it suffers several weaknesses [16,19,26], it is unlikely that misuse of the metric underlies the lack of evidence for greater evolvability under stress [13,14]. Nonetheless, it is always useful for studies to report not just heritability but also pheno-

typic mean and the components of heritability: phenotypic and additive genetic variances [16,19,26].

Univariate metrics of evolvability, such as heritability, might provide little insight into the evolutionary potential of complex phenotypes [27–30]. Differences among environments in the expression of genetic variation might not simply increase (or decrease) heritability, but rather change the relationships among traits. Evolution is intrinsically multivariate: selection acts on the whole organism, not individual traits in isolation, and traits share a genetic basis through pleiotropy. The additive genetic variance–covariance matrix, **G**, summarizes the multivariate genetic basis of multiple traits, potentially providing more informative evolvability metrics (Box 2).

Although understanding the evolutionary dynamics of **G** is a central aim in evolutionary biology [31], few studies have considered the intragenerational effect of environment. Available data indicate genetic relationships are affected by some, but not all, changes in environment

Box 2. Multivariate evolvability

The multivariate breeder’s equation, $\Delta\bar{z} = \mathbf{G}\beta$, describing intergenerational change in trait mean ($\Delta\bar{z}$) as a function of the selection gradient (β) and the additive genetic variance–covariance matrix (**G**), implicates **G** as a source of information about evolvability. There are currently no widely utilized multivariate evolvability metrics, although several possibilities exist. One possible metric is total variance (V_T [29,30]) (Figure 1a). However, as the sum of individual trait variances (the diagonals of **G**), V_T provides no more information than that obtained from individual traits. A shared genetic basis of traits (due to linkage or pleiotropy), as summarized by genetic covariances (off-diagonals of **G**), might limit evolvability, and this information needs to be captured by a multivariate evolvability metric [27–30].

The rank of **G** (the number of linearly independent rows) indicates how many multi-trait phenotypes are associated with genetic variation, and therefore whether all regions of trait space are evolutionarily accessible [28,29]. Although easily interpretable, statistical challenges involved in estimated rank make it a difficult metric to apply [28,29]. Even when of full rank **G** might be biased (genetic variation distributed unequally among multivariate traits), indicating not all regions of trait space are equally evolutionarily accessible. The

extent of bias in **G** can be summarized by the effective dimensionality (n_D , the sum of each eigenvalue divided by the largest eigenvalue) [29]. Evolvability is lower when the distribution of variance is more strongly biased (n_D is low) (Figure 1b). Similarly, Hansen and Houle [30] proposed autonomy (fraction of genetic variation that is independent of other traits) as an indicator of the potential for individual traits to evolve.

Metrics of evolvability are useful summaries of how populations might respond to unspecified selection pressures. However, the hypothesis that release of cryptic genetic variation in stressful or novel environments accelerates phenotypic adaptation must be tested by comparing the availability of genetic variation to the specific selection experienced in the novel or stressful environment. The strength and direction of selection (summarized by β , the linear selection gradient, or γ , the matrix of nonlinear selection gradients) can be estimated in different environments [28,35,44]. In each environment, we can then determine the genetic variance for the specific trait combination favored by selection, and test whether the expected response (evolvability) is greater from visible or cryptic genetic variation [28,30] (Figure 1c).

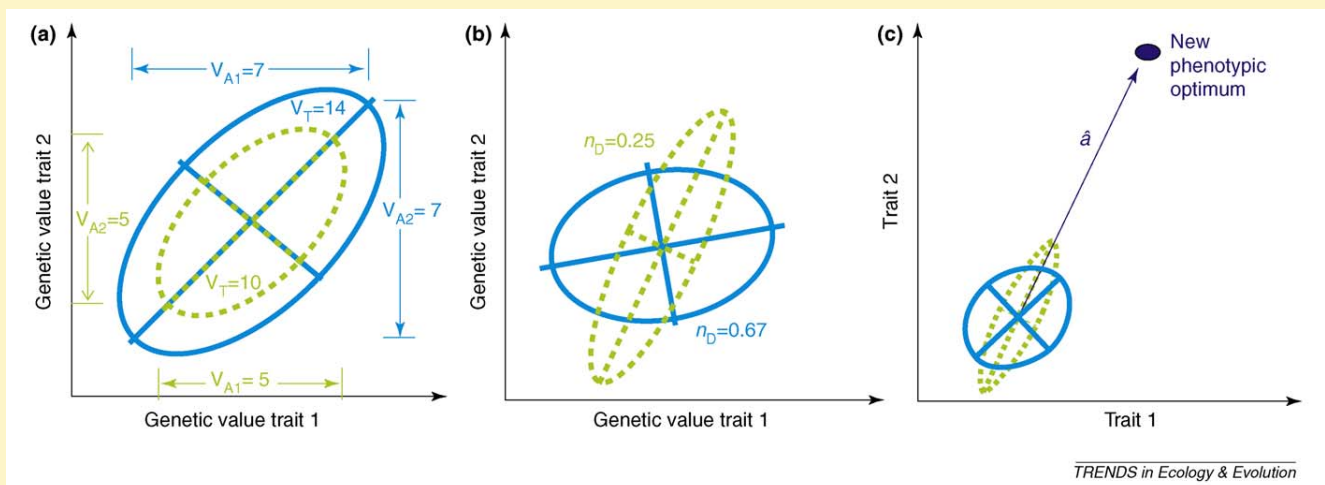


Figure 1. Schematic of evolvability inferred from **G** estimated in different environments. (a) Here the mean genetic values (the intersection of the crosshairs of each ellipse) and the genetic covariances (angle of the axes of each ellipse) are the same in both environments, but the total variance (size of the ellipse: $V_T = V_{A1} + V_{A2}$), and thus evolvability, is greater in the blue environment. (b) Both **G**s have the same mean genetic value and total variance, but differ in bias; the effective dimensionality (n_D), and thus evolvability, is higher in the blue environment. (c) Evolvability of the two **G**s illustrated in (b) in response to a specific selection pressure, depicted as the linear directional selection gradient, β . Here, the variance available to selection is less in the blue environment, despite the higher n_D .

Opinion

[32,33]. Unfortunately, as discussed by Hansen and Houle [30], methods employed to compare **G** allow inference of environmental differences but not how these affect evolvability (Box 2). Estimates of **G** in different environments need to be compared using appropriate methods (Box 2) to determine how multivariate evolvability varies with environment.

Is cryptic genetic variation necessary and sufficient for phenotypic evolution?

When viewed from the long-term perspective of the fossil record, phenotypic evolution appears to occur in bursts; periods of relatively rapid change are interspersed with periods of no change. Robustness and release of cryptic genetic variation in stressful or novel environments has been posited as an explanation of this pattern of saltatory evolution [5–7,10,11]. We argue there is little difference between evolutionary scenarios based on visible versus cryptic genetic variation. Evolutionary stasis might be due to robustness [6] or sustained stabilizing selection about an adaptive optimum [34], but in either case depends on the constancy of environments [27]. When the environment changes, phenotypic evolution occurs, whether owing to selection on visible genetic variation toward the new adaptive optimum [34] or to the release of cryptic genetic variation [6]. Differences in optimal phenotype among environments is the major diversifying force in evolution [34,35]. Leaving aside for the time being the question of what environments release cryptic genetic variation, here we consider two questions. First, does a lack of visible genetic variation prevent phenotypic adaptation to new (stressful) environments? Second, what is the evolutionary fate of released cryptic genetic variation?

Is visible genetic variation lacking?

Visible genetic variation has long been thought to be ubiquitous [36]. However, low visible additive genetic variation has recently been demonstrated in non-model species [28,37]. Sustained natural selection has been implicated as the cause of low visible genetic variation; variation is specifically lacking for the phenotypes under selection [28]. For example, there is little visible additive genetic variation for the combination of male sex pheromones favored by females of the Australian rainforest fly *Drosophila bunnanda* [38], and male pheromones are unable to evolve further in response to female mate choice [39]. However, although these studies suggest limited visible genetic variation might constrain phenotypic evolution in the current environment, they provide no insight into what happens when the environment, and the direction of selection, changes. We suggest that if selection depletes variation only for the specific phenotypes under selection, then visible additive genetic variation might typically be available for adaptation toward new adaptive optima. Returning to the *D. bunnanda* example, there is abundant visible genetic variation for combinations of male pheromones that do not affect fitness in the current environment [38]. If the direction of selection (the pheromone blend favored by females) changed, male pheromones could therefore evolve.

Evolutionary fate of cryptic genetic variation

Response to artificial selection on phenotypes revealed by some experimental manipulations [6,9] provides strong evidence that cryptic genetic variation exists, but no insight into the role it plays in phenotypic evolution in the wild [40]. Once released, the fate of cryptic genetic variation depends on the fitness of the revealed phenotypes. Although we have emphasized the hypothesis that changes in selection release cryptic genetic variation (Box 1), it remains to be determined whether phenotypes revealed by environmental change are under selection (i.e. affect fitness). For example, sensory bristle number in *Drosophila* is robust and certain environments release cryptic genetic variation [6,41], but there is no compelling evidence that bristle number affects fitness [41]. Release of cryptic genetic variation for selectively neutral phenotypes might result in phenotypic evolution through random genetic drift, depending on population size and allele frequencies.

If cryptic genetic variation is released for traits that affect fitness, it will be purged or fixed depending on whether it is deleterious or beneficial. Much of the released cryptic genetic variation seems unlikely to be fit in any environment [9] and, although fitness has rarely been explicitly estimated, available data support this expectation with released cryptic genetic variation typically [24,42], but not always [42], unfit. The argument can always be made that released cryptic genetic variation might be fit in some environments, an untestable hypothesis as we cannot predict all possible directions of selection a population might be subject to in the future [7]. We argue that it is most pertinent to ask whether cryptic genetic variation is fit in the environment where it is released. If we are unable to demonstrate high fitness of cryptic genetic variation in the releasing environment, it argues against a general role of cryptic genetic variation in adaptive phenotypic evolution.

In an Australian rainforest fly, *Drosophila birchii*, van Heerwaarden and colleagues [43] used inbreeding to release cryptic genetic variation, and artificial selection mimicking ecological variation to determine whether the released variation could break an evolutionary constraint. Visible additive genetic variation for desiccation resistance is very low in *D. birchii*, which might account for its limited geographic range and present an extinction risk in the face of climate change [37]. Visible genetic variation for desiccation resistance increased with inbreeding, but the populations did not respond to selection for improved desiccation resistance [43]. This experiment demonstrates that we cannot assume that increased heritability of a trait following disruption of robustness will result in evolution of the trait.

Future research contrasting visible and cryptic genetic variation

We suggest that whether visible genetic variation constrains adaptation to novel or stressful environments, and whether released cryptic genetic variation promotes adaptation to these environments, remain open questions [28,30,40,44]. Resolving these questions relies on further empirical study (Box 3). Use of experimental evolution to

Box 3. Questions to be addressed and approaches to be taken

Research interest in robustness and cryptic genetic variation has focused on understanding how cryptic genetic variation is stored [2], and little progress has been made in determining how released cryptic genetic variation might affect phenotypic evolution [40]. Here we have identified three general areas that need to be addressed.

Evolvability is determined by environment

We have argued that there is currently no compelling evidence that stressful or novel environments release cryptic genetic variation and increase evolvability. Resolving this issue will depend on:

- Statistically robust comparisons of the distribution of phenotypic and additive genetic variation among environments.
- Consideration of a range of diverse taxa and traits across a continuum of ecologically relevant environments.
- Broadened definition of evolvability to take into account how genetic variation contributes to phenotypic evolution.

Cryptic genetic variation is necessary and sufficient for phenotypic adaptation to novel or stressful environments

Distinguishing between possible causes of evolutionary stasis and change depends on:

- Robust statistical comparisons of visible and released cryptic genetic variation, and of the selection acting on the traits of interest in environments where the expression of genetic variation differs. Such comparisons can determine whether genetic variation (visible or cryptic) is available (or lacking) for the specific phenotypes under selection.
- Experimental evolution in stressful or novel environments from visible or cryptic genetic variation to test whether visible genetic variation constrains evolution whereas cryptic genetic variation promotes it.
- Drawing general conclusions depends on data from a range of taxa, traits and environments.

Cryptic genetic variation underlies the evolution of novelties

Because it evolves neutrally, cryptic genetic variation is expected to explore regions of trait space not accessible under selection. Evidence for this will come from:

- Robust statistical demonstrations that cryptic genetic variation is more autonomous than visible genetic variation.
- Experimental evolution addressing whether novel complex phenotypes contained within cryptic genetic variation evolve or are inherently unfit.

compare rates of phenotypic evolution from cryptic versus visible genetic variation is problematic, because the environment both releases cryptic genetic variation and applies selection [45]. Such experiments might be possible in some taxa where release of cryptic variation can be decoupled from the selection environment (e.g. [37,46]; see also Refs [7,35]).

An alternative approach is to compare visible versus cryptic evolvability of a population to specific selection regimes [28,30]. This requires estimation of both visible and cryptic G , and of selection in different environments (Box 2), to compare predicted rates of evolution [28,30]. Consideration of a range of taxa and traits is necessary to identify general trends and infer whether release of cryptic genetic variation plays an important role in phenotypic diversification (Box 3).

Is cryptic genetic variation enriched for evolutionary novelties?

The evolutionary origins of complex novel phenotypes, a classic example of which is the eye, are contentious. How

can fixation of new mutations by selection generate such phenotypes if intermediate forms are unfit? Because it is protected from selection, and thus the requisite of fit intermediaries, cryptic genetic variation is expected to facilitate the evolution of novel complex phenotypes [1–3,7]. Several recent experiments have demonstrated that release of cryptic genetic variation can facilitate evolution of novelties at the molecular level [47]. Here we ask what the study of cryptic genetic variation can tell us about how phenotypic novelties might evolve.

The hypothesis that cryptic genetic variation is enriched for novel trait combinations leads us to the explicit empirical prediction that cryptic genetic variation will have greater autonomy than visible genetic variation (Box 2). There is little data on differences between cryptic and visible genetic variation [2], although several studies have demonstrated lower genetic correlations in environments designated as novel [14], suggesting cryptic genetic variation might indeed be most autonomous. Autonomy suggests traits can respond independently to selection, but also that pleiotropic variation might exist for a range of different multivariate phenotypes, potentially accelerating the response to multivariate selection [27,30].

A mismatch in autonomy between cryptic and expressed genetic variation suggests selection acts on visible genetic variation to alter the distribution of pleiotropic effects [48,49]. Pleiotropy will affect the evolution of traits that are themselves the direct target of selection, but also any trait that shares genetic variation with fitness [50]. Cryptic genetic variation might be enriched for alleles with detrimental pleiotropic effects on fitness, and therefore be rapidly purged by selection when released [27,30] (but see Ref. [8]). The evolutionary fate of released cryptic genetic variation, and whether this is due to direct or apparent (pleiotropic) selection, await empirical determination.

Conclusions

Robustness, and its corollary, cryptic genetic variation, are typical of many traits and populations, and must be taken into consideration if we are to understand phenotypic evolution. It has been suggested that the release of cryptic genetic variation in stressful environments underlies macro-evolutionary patterns. However, a contribution of released cryptic genetic variation to phenotypic evolution cannot be assumed, and awaits empirical testing. We need first to determine how the environment alters the distribution of phenotypic and additive genetic variation. We can then ask how the altered distribution affects the ability of the population to respond to the new selection environment, and whether released cryptic genetic variation is fixed or lost through selection. Applying existing analytical tools to these questions, we can move beyond descriptions of cryptic genetic variation to address its role in phenotypic evolution.

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