EVOLUTION Evolvability predicts macroevolution under fluctuating selection

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Heritable variation is a prerequisite for evolutionary change, but the relevance of genetic constraints on macroevolutionary timescales is debated. By using two datasets on fossil and contemporary taxa, we show that evolutionary divergence among populations, and to a lesser extent among species, increases with microevolutionary evolvability. We evaluate and reject several hypotheses to explain this relationship and propose that an effect of evolvability on population and species divergence can be explained by the influence of genetic constraints on the ability of populations to track rapid, stationary environmental fluctuations.

key insight from the modern synthesis of evolutionary biology was that response to selection, and therefore adaptation, depends on the presence of genetic variation. This led to the idea that more genetically diverse populations and species should be able to adapt faster when their environment changes. Simpson (1) in the 1940s was the first to test this prediction, but he failed to detect differences in levels of variation between slow- and fast-evolving lineages. Thirty years later, Kluge and Kerfoot (2) reported a positive correlation between within-population variation and among-population differentiation in seven vertebrate species. However, their study was criticized on methodological grounds (3, 4), casting doubt on what became known as the "Kluge-Kerfoot phenomenon." Following the emergence of evolutionary quantitative genetics in the 1980s, the focus shifted from phenotypic to genetic variation, and studies started relating patterns of multivariate additive genetic variance (evolvability) to patterns of phenotypic divergence. The results have been mixed, however (5-18), and marred by persistent methodological problems related to the quantification of evolvability, divergence, and their relationship (19-21). Amending some of these problems, two recent synthetic studies (17, 21) have concluded that multivariate microevolutionary evolvability relates to evolution on longer timescales within many study systems, but how general this relationship is and what generates it remain unknown.

To investigate the divergence-evolvability relationship and evaluate various biological and methodological hypotheses put forward to

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explain it, we gathered two extensive datasets on contemporary and fossil taxa. For the contemporary taxa, evolvability estimated as within-population mean-scaled additive genetic variance (22, 23) is combined with trait divergence based on 2011 population means from 280 traits in 33 species and 676 species means from 130 traits in 96 different species. For the fossil taxa, evolvability estimated from mean-scaled within-sample variance is combined with changes in trait means across time in 589 fossil time series from 150 independent lineages for a total of 10,594 samples. The time of divergence between fossil samples ranges from 10 years to 7.6 million years.

The two datasets offer complementary strengths and unprecedented insights into the mechanisms that can generate a relationship between evolvability and divergence among taxa. The contemporary data provide direct measures of evolvability based on additive genetic variance in a wide variety of traits, but the not known, which limits information al the causal interplay between evolvability and divergence. The fossil time-series data allow investigation of the dynamic relationship between divergence and evolvability through time but lack direct information about genetic variation. We mitigate this shortcoming by documenting a strong and near-isometric scaling relationship between measures of additive and phenotypic variance observed across traits in the contemporary data (Fig. 1) and use this to translate phenotypic variation within fossil samples into estimates of evolvability.

Relationship between divergence and evolvability

Higher evolvability is systematically associated with more divergence among populations, species, and fossil samples (Fig. 2). Variation in evolvability explains 30% of the among-population divergence, 12% of the among-species divergence, and 37% of the samples within a fossil time series divergence. The scaling between divergence and evolvability is similar in the contemporarypopulation and fossil data, with a 1% increase in evolvability predicting a $0.46 \pm 0.05\%$ increase in among-population divergence and a 0.42 \pm 0.04% increase in divergence among fossil samples. For the contemporary-species data, a 1% increase in evolvability predicts a 0.36 \pm 0.08% increase in among-species divergence.

The fossil time series further allows for causal analysis, in which the evolvability of each fossil sample is used to predict the evolutionarv change to the next sample (Fig. 3A). As for divergence measured at the time-series level, morphological distance between consecutive samples scales positively with evolvability (Fig. 3B). Our results show that an increase

Fig. 1. Isometric scaling between phenotypic and genetic variation. Mean-

scaled genetic variance, evolvability (e_{μ}) , expressed as percent evolutionary change regressed against mean-scaled phenotypic variance ($p_{\mu} \times 100$). For the morphological traits (purple line, n =527), $\ln(e_{11}) = -1.10 (\pm 0.08) + 0.99$ $(\pm 0.02) \ln(p_{\mu})$ and $R^2 = 83\%$. For all traits (orange line, n = 669), $\ln(e_{\mu}) =$ $-1.24 (\pm 0.08) + 0.96 (\pm 0.02) \ln(p_{\mu})$ and $R^2 = 81\%$. The coefficients are obtained from least-squares regressions fitted to log-transformed variables, and the slopes ± SE are corrected for attenuation (= 0.6%) due to estimation error in the phenotypic variance. The dashed line shows isometric scaling. We used the exponent of the intercept (-1.1)



from the morphological regression as an estimate of heritability, $h^2 = e^{-1.1} = 0.33$, and used this to predict evolvabilities from phenotypic variances in the fossil data. The near isometry and high R^2 make this a good prediction over the range of the data.

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in evolvability of 1% is associated with a 0.40 \pm 0.02% increase in the magnitude of divergence between consecutive samples, explaining 17% of the variance. This relationship is not driven by differences among time series, as the average within-time-series relationship was of comparable magnitude: $0.36 \pm 0.02\%$. It could be an artifact, however, of within-sample variation (i.e., evolvability) being confounded by microevolution within the samples. To account for this, we fitted an Ornstein-Uhlenbeck process to each time series and used this to predict and remove within-sample variance due to microevolution of the trait mean. Because we did not have the exact duration of each fossil sample, we considered a worst-case scenario in which the within-sample time interval equals 50% of the maximum possible duration, that is, when there is no temporal gap between successive samples (24). Under such conditions, a 1% increase in corrected evolvability estimates is still associated with a $0.30 \pm 0.02\%$ increase in the magnitude of changes in the trait mean, explaining 11% of the variance (fig. S1D). A more realistic, yet still exaggerated, scenario in which the fossil samples are assumed to span 10% of the maximum duration gives an increase of $0.37 \pm 0.02\%$ explaining 15% of the variance (fig. S1C), which is almost identical to the uncorrected result.

We compiled and developed various hypotheses to investigate potential mechanisms that could generate a correlation between evolvability and divergence on micro- and macroevolutionary timescales (table S1). After rejecting several noncausal hypotheses involving statistical artifacts, gene flow, plasticity, and selection shaping genetic variation to align with lines of population divergence (concordant selection), we turned to causal hypotheses. We first argue that the relationship is not a simple consequence of lack of genetic variation limiting evolution under directional selection or genetic drift; then we propose an alternative hypothesis based on genetic constraints limiting evolutionary responses to rapidly fluctuating selection.

Rejection of noncausal explanations for divergence-evolvability correlations Spurious correlation

The regression of inter- on intrapopulation variation can be subject to statistical artifacts arising from (i) the use of the same or related variables at both levels (4); (ii) a correlation between within-sample variance, which is related to estimated evolvability, and estimation variance in the means, which will bias estimates of among-population variance; (iii) a correlation between estimation variances of evolvabilities and means; and (iv) heterogeneity in the data. The first problem, which was a source of criticisms of Kluge and Kerfoot, does not apply to our analysis, because we used population means to scale measures of evolvability and log transformation to measure divergence on a proportional scale.

The second problem can be eliminated by correcting among-population divergence for bias. Analyzing a subset of the data for which bias correction was possible revealed no qualitative differences compared with our main results (figs. S2 and S3). As for the third problem, we show in fig. S4 that correlated estimation variances in means and variances do not cause a spurious correlation.

Correlations may also arise because both inter- and intrapopulation variances depend on trait type and dimensionality (25). This can be rejected as an explanation for our general result because divergence-evolvability relationships are similar within homogeneous trait categories (Fig. 4, A to F).

Gene flow

Gene flow among populations may generate a divergence-evolvability relationship because intro-

gression among more-divergent populations could generate more genetic variation within populations (26) and because high evolvability could counteract maladaptation and homogenization of populations owing to gene flow (27, 28). Although this mechanism could contribute to the stronger relationship between divergence and evolvability at the population level than at the species level, we reject the gene-flow hypothesis as a general explanation because it cannot generate the divergenceevolvability relationship observed across temporally separated fossil samples.

Phenotypic plasticity

Nongenetic responses to environmental changes (plasticity) often constitute a substantial component of population differences (29) that may correlate with evolvability across traits within populations (30-32). We reject this as a general explanation, because a strong evolvability-divergence relationship remains in data from common-garden designs that reduce plasticity [Fig. 4, G to I; see also Opedal *et al.* (17)]. We cannot exclude a minor role for plasticity, however, because the relationship is slightly shallower in the common-garden data.

Concordant selection

A divergence-evolvability correlation could arise if the episodes of directional selection that drive divergence are concordant with patterns of stabilizing selection molding genetic variance within populations (7, 33–35). In this case, differences in population evolvability would not be the cause of differences in divergence and would therefore not be causally relevant to macroevolution. Although relevant empirical estimates of stabilizing selection are lacking, this hypothesis can be rejected on the basis of inconsistencies with some of our empirical findings and on theoretical grounds.

Fig. 2. Evolvability predicts divergence among populations, species, and

fossil samples. Divergence (d) is the average percent change in magnitude from the trait grand mean (24). Evolvability (e_{ii}) is the mean-scaled additive genetic variance expressed as predicted percent evolutionary change under unit selection. For the fossil data, evolvability is predicted by multiplying the sample variance by the heritability ($h^2 = 0.33$) obtained in Fig. 1. The scaling exponents ($b \pm SE$) and marginal R^2 (%) are obtained from mixed-effect models fitted to log-transformed variables and are corrected for an attenuation bias of 13, 17, and 12% for the population (n = 271), species (n = 130), and fossil data (n = 589), respectively.





 $b = 0.40 \pm 0.02 (17\%)$... $\overline{b}_w = 0.36 \pm 0.02$ Horizontal distance of the second dis

Fig. 3. Evolvability predicts divergence between consecutive fossil samples. (A) An example of a fossil time series from Grey *et al.* (55), for which sample means of shell area of the ostracod *Velatomorpha altilis* are shown across time elapsed since the oldest sample (bars indicate sample standard deviation). We converted sample variances into estimates of evolvability (e_{μ}) as explained in Fig. 1 and used these to predict the absolute morphological distance to the next sample on log scale (see inset). Sample 1 (dark blue) has a large variance, and there is a large difference between the mean shell area of

sample 1 and sample 2. Hence, the evolvability of sample 1 and the absolute morphological distance from sample 2 correspond to the point in the upperright corner of the inset. myr, million years. (**B**) Plot showing the relationship between evolvability and absolute morphological distance to the next sample for all cases with a sample size of at least 30 specimens (n = 5009). The slope ($b \pm SE$) and marginal R^2 (%) are obtained from a mixed-effect model fitted to log-transformed variables. The dashed line shows the average within–time-series slope ($\bar{b}_w \pm SE$). Both slopes $\pm SE$ are corrected for a 2.1% attenuation bias.

First, molding genetic architecture by stabilizing selection is likely to take time, and we would therefore expect the scaling relationship among species to be as strong as—if not stronger than—that among populations. The weaker divergence-evolvability relationship at the amongspecies level contradicts this prediction.

Second, stabilizing selection is likely to reduce additive genetic variation more than environmental variation because the latter is not transmitted through generations. We would therefore expect a relationship between heritability and divergence, which is absent (fig. S5).

The concordance hypothesis is also theoretically problematic because it requires an implausible range of variation in strengths of stabilizing selection. Assuming a standard model for maintenance of genetic variance in a balance between mutation and stabilizing selection (36), we show that the strength of stabilizing selection needs to vary over at least four orders of magnitude, and likely more, to account for the observed scaling between evolvability and divergence (fig. S6). This would cover a range from inefficiently weak to unrealistically strong selection. Such range in stabilizing selection is even more unlikely to explain the within-trait scaling relationship between evolvability and divergence observed in the fossil time series (Fig. 3).

An alternative version of the concordance hypothesis is that within-population variation is shaped not by mutation-selection balance but by canalizing selection changing the effects of alleles (rather than their frequencies) to match the fitness landscape. This is even less plausible, however, because canalizing selection is weak, nonlinearly related to patterns of selection on the phenotype, and largely determined by patterns of epistasis (37-39). Most salient, strong stabilizing selection makes canalization less effective than intermediate strengths of selection, rendering a close match between evolvability and the curvature of the fitness landscape unlikely even under ideal conditions. Combining this with the similarly complex and nonlinear relationship between mutational effects and segregating genetic variance (40), we reject canalization as a general explanation for a regular relationship between divergence and evolvability.

Causal explanations for divergenceevolvability correlations Neutral evolution

In the absence of selection, trait divergence is expected to scale proportionally with evolvability and linearly with time due to genetic drift (41, 42). We reject this hypothesis because divergence in our data does not accumulate with time (fig. S7A), and on longer timescales, rates of evolution become much too slow to be explained by either the standard drift model (41) or the mutation-drift model (42, 43) [Fig. 5A; see also (33, 44–49)].

Directional selection and genetic constraints

If population divergence reflects patterns of directional selection, the genetic-constraints

hypothesis (7, 50) predicts more divergence along directions with more genetic variation and therefore a positive relationship between divergence and evolvability (19). Given enough time, however, populations would reach their optima, and the relationship between divergence and evolvability should vanish (7). This prediction is supported by our finding of a weaker relationship at the species level than at the population level, as well as the strong signal in the fossil data for which the timescale is comparable to population divergence. It is also supported by the fact that low-evolvability traits have diverged less among populations than among species, while divergence of high-evolvability traits is similar at both levels (Fig. 2).

Nevertheless, estimated evolvabilities are too large to substantially constrain directional selection on the timescales considered. Indeed, only 29 generations would be necessary to generate the median divergence magnitude of 5% observed in the fossil data for a trait with a moderate evolvability under moderate selection (24, 51). This time span is much shorter than the median of 35,115 years between our fossil samples.

Pleiotropic constraints

The genetic-constraints hypothesis could be rescued if the true potential for evolution were much lower than indicated by estimated evolvabilities. This could come about through constraining selection on genetically correlated traits (*52*). Such constraints can be quantified with conditional evolvability, that is,



Fig. 4. The divergence-evolvability relationship across different trait types and environments. (A to I) The magnitude of divergence (*d*) is the expected percent change of a population, species, or fossil sample from the trait grand mean. Evolvability (e_{μ}) is the mean-scaled additive genetic variance expressed as percent evolutionary change under unit

selection. For the fossil data, evolvability is predicted by multiplying the sample variance by the heritability ($h^2 = 0.33$) obtained in Fig. 1. The scaling exponents ($b \pm SE$) are the slopes from the log-log regression from each group corrected for attenuation bias. The R^2 (%) is given in parentheses.

the evolvability of a focal character when other genetically correlated characters are kept constant (53, 54). If conditional evolvabilities are much smaller than unconditional evolvabilities but show similar patterns of variation across traits, then genetic constraints may influence evolution on longer timescales and explain the relationship between divergence and unconditional evolvabilities. We provide a partial test of this hypothesis by conditioning evolvabilities on overall size of the organism in a subset of 25 G-matrices from animal species in the contemporary data. Conditioning on size reduces the median evolvability by 43% and reveals a strong correlation between conditional and unconditional evolvabilities [fig. S8; coefficient of determination (R^2) = 87%]. Although a reduction of 43% is by itself insufficient to cause substantial genetic constraints under directional selection, it is possible that conditioning on more aspects of the organism than just size would reduce the evolvability of focal traits more drastically. This would increase the viability of the genetic-constraints hypothesis beyond microevolutionary time-

scales and could explain some of the observed divergence-evolvability relationship.

Fluctuating selection and genetic constraints

Genetic constraints could also influence divergence if the evolutionary timescale is very short. Evolution is not a rectilinear process, and on timescales shorter than a million years or so, it mostly takes the form of bounded fluctuations with a constant (stationary) distribution so that evolutionary changes do not accumulate with time (44, 45) (fig. S7A). This is likely caused by populations tracking adaptive optima that





Fig. 5. Stationary fluctuations in optima and traits. (**A**) Rate of evolution (magnitude of change per year) against the time interval between two consecutive samples in the fossil data (n = 6231). The magnitude of change (d_c) is corrected for estimation error in the sample means (24). The scaling exponent, $b \pm SE$ (R^2), is the slope of the least-squares regression on log-transformed data. Also represented are regression lines predicted by neutral evolution (light blue, scaling exponent = -0.5) and directional selection (dark blue, scaling exponent = 0) that are fitted to the data with an intercept at the grand mean of both variables and a slope set to the theoretical prediction (44, 46–48). The prediction for the fluctuating-selection model (orange) is based on an Ornstein-Uhlenbeck model with parameters fitted using a grid search (24) (fig. S6B), where the half-lives of the return rate of the optimum (α) and the

tracking rate of the population mean (*r*) are ln(2)/ α = 1 year and ln(2)/*r* = 30.5 years, respectively. (**B**) Simulation showing evolutionary changes in the trait mean of two populations with different evolvabilities tracking a fluctuating optimum (gray curve). The half-life of the return rate of the optimum to its central value is set to 30 years (fig. S6B). If we assume that one generation equals 1 year, then keeping $r \le \alpha$ requires r < 0.023 per generation. Because *r* equals the evolvability multiplied by the mean-scaled quadratic selection gradient around the optimum, γ , we can compute that an evolvability of 0.56% (the median of our data) would require $|\gamma| < 4.1$ to keep r < 0.023. With this value of γ , a 10% trait shift from the optimum reduces fitness by 2%. Population 1 (light-blue curve) has an evolvability of 0.01% and hence a slower tracking rate ($r = \gamma e_{\mu}$) of the optimum and smaller fluctuations in the trait mean than population 2 ($e_{\mu} = 0.1\%$; purple curve).

fluctuate within a limited range. Under this scenario, traits with low evolvabilities would lag further behind their optima and change less than traits with higher evolvabilities, as illustrated in Fig. 5B. To explore whether such dynamics could rescue a version of the genetic-constraints hypothesis, we show [(24); on the basis of (14)]that with stationary fluctuations, the predicted variance in the log trait mean would be D = Vr/ $(r + \alpha)$, where r is the tracking rate of adaptation, and V and α are the stationary variance and the return rate of the fluctuating optimum, respectively. Because the tracking rate is proportional to evolvability, we predict a positive relationship between divergence and evolvability when the tracking rate is equal to or slower than the rate of environmental fluctuations (14, 24).

Fitting this model to the combined fossil time-series data revealed predominantly stationary dynamics and returned high rates of both tracking and fluctuations in the optimum, with plausible half-lives in the range from one to up to a hundred years at most (Fig. 5A and fig. S7B). As can be seen from the likelihood surface (fig. S7B), the fitted model is symmetric for *r* and α and cannot tell whether *r* is smaller or larger than α . Nevertheless, as illustrated in Fig. 5B, our estimated evolvabilities combined with reasonable strengths of selection will often generate tracking rates in the range of

tens and hundreds of generations, making it plausible that adaptation is slower than at least part of the environmental fluctuations of the optimum and able to influence the extent of fluctuations in the trait mean.

Hence, tracking fast stationary fluctuations in optima can plausibly account for an effect of evolvability on evolutionary divergence in both extant and extinct populations. On timescales longer than a million years, divergence may start to accumulate, and evolution may include rare bursts of change to new adaptive zones (1, 45). Even so, rapid stationary fluctuations would still constitute a component of the among-species variance (45) and could therefore explain an influence of evolvability on this level also. This is in line with the weaker relationship between divergence and evolvability observed in the contemporary species data. Note, however, that this model would not generate a phylogenetic signal by itself, and it cannot explain the strong association between evolvability and rates of evolution across million-year timescales found in studies of homogeneous morphological traits such as dipteran wings, which are dominated by nonstationary Brownian motion-like evolution (15, 18).

Conclusions

With two large and independent datasets, we have established the existence of a positive scal-

ing relationship between evolutionary divergence and evolvability, thus providing a link between micro- and macroevolution. After eliminating alternative explanations, we conclude that this pattern most plausibly results from genetic constraints on evolution under rapid stationary fluctuations. We have shown that if stabilizing selection around optima is not too strong, even high observed evolvabilities may cause constraints limiting trait fluctuations. If pleiotropic constraints further reduce evolvability along directions of selection, stronger selection and/or slower fluctuations of optima can be accommodated, leaving genetic constraints on stationary fluctuations a robust explanation for the divergence-evolvability relationship.

REFERENCES AND NOTES

- G. G. Simpson, Tempo and Mode in Evolution (Columbia Univ. Press, 1944).
- 2. A. G. Kluge, W. C. Kerfoot, Am. Nat. 107, 426–442 (1973).
- 3. R. R. Sokal, *Am. Nat.* **110**, 1077–1091 (1976). 4. F. I. Rohlf, A. J. Gilmartin, G. Hart, *Evolution* **37**, 180.
- F. J. Rohlf, A. J. Gilmartin, G. Hart, *Evolution* **37**, 180–202 (1983).
- 5. D. Lofsvold, Evolution 42, 54–67 (1988).
- 6. D. L. Venable, M. A. Búrquez, Evolution 44, 1748–1763 (1990).
- 7. D. Schluter, Evolution **50**, 1766–1774 (1996).
- 8. S. Andersson, Biol. J. Linn. Soc. 62, 519–532 (1997).
- 9. A. V. Badyaev, G. E. Hill, Evolution 54, 1784–1794 (2000).
- 10. G. Marroig, J. M. Cheverud, Evolution 59, 1128-1142 (2005)
- S. F. Chenoweth, M. W. Blows, *Evolution* 62, 1437–1449 (2008).

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- 12. P. A. Hohenlohe, S. J. Arnold, Am. Nat. 171, 366-385 (2008).
- 13. C. B. Kimmel et al., Evolution 66, 419-434 (2012).
- 14. G. H. Bolstad et al., Philos. Trans. R. Soc. London Ser. B 369, 20130255 (2014).
- 15. D. Houle, G. H. Bolstad, K. van der Linde, T. F. Hansen, Nature 548, 447-450 (2017).
- 16. J. W. McGlothlin et al., Evol. Lett. 2, 310-322 (2018).
- 17. Ø. H. Opedal et al., Proc. Natl. Acad. Sci. U.S.A. 120, e2203228120 (2023)
- 18. P. T. Rohner, D. Berger, Proc. Natl. Acad. Sci. U.S.A. 120. e2211210120 (2023).
- 19. T. F. Hansen, D. Houle, J. Evol. Biol. 21, 1201-1219 (2008).
- 20. T. F. Hansen, K. L. Voje, Evolution 65, 1821-1822 (2011).
- 21. K. L. Voje et al., in Evolvability: A Unifying Concept in Evolutionary Biology?, T. F. Hansen, D. Houle, M. Pavličev,
- C. Pélabon, Eds. (MIT Press, 2023), chap. 14, pp. 289-306. 22. D. Houle, Genetics 130, 195-204 (1992).
- 23. T. F. Hansen, C. Pélabon, W. S. Armbruster, M. L. Carlson,
- J. Evol. Biol. 16, 754-766 (2003). 24. Materials and methods are available as supplementary materials
- 25. R. Lande, Syst. Zool. 26, 214-217 (1977).
- 26. F. Guillaume, M. C. Whitlock, Evolution 61, 2398-2409
- (2007).
- 27. M. G. Bulmer, The Mathematical Theory of Quantitative Genetics (Clarendon Press, 1980).
- 28 | Tufto Genet Res 76 285-293 (2000)
- 29. M. A. Stamp, J. D. Hadfield, Ecol. Lett. 23, 1432-1441 (2020).
- 30. D. W. A. Noble, R. Radersma, T. Uller, Proc. Natl. Acad. Sci. U.S.A. 116, 13452-13461 (2019).
- 31. R. Radersma, D. W. A. Noble, T. Uller, Evol. Lett. 4, 360-370 (2020).
- 32. F. Johansson, P. C. Watts, S. Sniegula, D. Berger, Evolution 75, 464-475 (2021).
- 33. S. J. Arnold, Am. Nat. 183, 729-746 (2014).
- 34. W. Armbruster, K. Schwaegerle, J. Evol. Biol. 9, 261-276 (1996).

- 35. S. J. Arnold, M. E. Pfrender, A. G. Jones, Genetica 112, 9-32 (2001).
- 36. R. Lande, Genetics 94, 203-215 (1980).
- 37. T. F. Hansen, J. M. Álvarez-Castro, A. J. R. Carter, J. Hermisson, G. P. Wagner, Evolution 60, 1523-1536 (2006).
- 38. A. Le Rouzic, J. M. Álvarez-Castro, T. F. Hansen, Evol. Biol. 40, 317-340 (2013)
- 39. T. F. Hansen, G. P. Wagner, in Evolvability: A Unifying Concept in Evolutionary Biology?, T. F. Hansen, D. Houle, M. Pavličev, C. Pélabon, Eds. (MIT Press, 2023), chap. 7, pp. 121-146.
- 40. T. F. Hansen, in Evolvability: A Unifying Concept in Evolutionary Biology?, T. F. Hansen, D. Houle, M. Pavličev, C. Pélabon, Eds. (MIT Press, 2023), chap. 5, pp. 73-100.
- 41. R. Lande, Evolution 30, 314-334 (1976).
- 42. M. Lynch, W. G. Hill, Evolution 40, 915-935 (1986).
- 43. M. Lynch, Am. Nat. 136, 727-741 (1990).
- 44. S. Estes, S. J. Arnold, Am. Nat. 169, 227-244 (2007).
- 45. J. C. Uyeda, T. F. Hansen, S. J. Arnold, J. Pienaar, Proc. Natl. Acad. Sci. U.S.A. 108, 15908-15913 (2011).
- 46. P. D. Gingerich, Science 222, 159-161 (1983).
- 47. P. D. Gingerich, Genetica 112, 127-144 (2001)
- 48. P. D. Gingerich, Annu. Rev. Ecol. Evol. Syst. 40, 657-675 (2009).
- 49. L. J. Harmon et al., Annu. Rev. Ecol. Evol. Syst. 52, 587-609 (2021).
- 50. S. J. Arnold, Am. Nat. 140 (suppl. 1), S85-S107 (1992)
- 51. J. Hereford, T. F. Hansen, D. Houle, Evolution 58, 2133-2143
- (2004). 52. T. F. Hansen, D. Houle, in Phenotypic Integration: Studying the
- Ecology and Evolution of Complex Phenotypes, M. Pigliucci, K. Preston, Eds. (Oxford Univ. Press, 2004), pp. 130-150. 53. T. F. Hansen, W. S. Armbruster, M. L. Carlson, C. Pélabon,
- J. Exp. Zool. B Mol. Dev. Evol. 296B, 23-39 (2003) 54. T. F. Hansen, T. M. Solvin, M. Pavlicev, Evolution 73, 689-703
- (2019).
- 55. M. Grey, Z. V. Finkel, P. K. Pufahl, L. M. Reid, Lethaia 45, 615-623 (2012).
- 56. A. Holstad et al., Data from: Evolvability predicts macroevolution under fluctuating selection [Dataset], Dryad (2024): https://doi.org/10.5061/drvad.4i0zpc8hx.

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SUPPLEMENTARY MATERIALS

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