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REVIEW

SPECIAL ISSUE

DEVELOPMENTAL PLASTICITY: FROM MECHANISMS TO EVOLUTIONARY PROCESSES

Spatial covariation between genetic and epigenetic diversity in wild plant and animal populations: a meta-analysis

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ABSTRACT

Epigenetic variation may be crucial in understanding the structure of wild populations, thereby aiding in their management and conservation. However, the relationship between epigenetic and genetic variation remains poorly understood, especially in wild populations. To address this, we conducted a meta-analysis of studies that examined the genetic and epigenetic structures of wild plant and animal populations. We aimed to determine whether epigenetic variation is spatially independent of genetic variation in the wild and to highlight the conditions under which epigenetic variation might be informative. We show a significant positive correlation between genetic and epigenetic pairwise differentiation, indicating that in wild populations, epigenetic diversity is closely linked to genetic differentiation. The correlation was weaker for population pairs that were weakly differentiated genetically, suggesting that in such cases, epigenetic marks might be independent of genetic marks. Additionally, we found that global levels of genetic and epigenetic differentiation were similar across plant and animal populations, except when populations were weakly differentiated genetically. In such cases, epigenetic differentiation was either higher or lower than genetic differentiation. Our results suggest that epigenetic information is particularly relevant in populations that have recently diverged genetically or are connected by gene flow. Future studies should consider the genetic structure of populations when inferring the role of epigenetic diversity in local adaptation in wild populations. Furthermore, there is a need to identify the factors that sustain the links between genetic and epigenetic diversity to improve our understanding of the interplay between these two forms of variation in wild populations.

KEY WORDS: Adaptation, Conservation, Epigenetics, Methylation

Introduction

Population adaptation to environmental constraints is a complex process involving both genetic and non-genetic variation. Genetic variation is critical in the ecological and evolutionary dynamics of populations, as it underlies population adaptation to external constraints through the process of natural selection, which increases a population's overall fitness. Under this process, individuals with genetic variants coding for the most adapted phenotype survive under particular environmental conditions, and these variants are then passed on to subsequent generations. However, genetic inheritance alone does not account for the transmission of phenotypic variation, and there are other non-genetic modes of inheritance, such as epigenetic modifications (Danchin and Wagner, 2010; Danchin et al., 2011; Mameli, 2004). Epigenetic modifications can be broadly defined as changes in gene expression (and hence phenotypes) that are not caused by changes in the DNA nucleotide sequence (Guil and Esteller, 2009; Richards, 2006). Examples of epigenetic modifications include DNA methylation, histone tail modifications and small RNAs (Allis and Jenuwein, 2016; Norouzitallab et al., 2019). For instance, DNA methylation consists of the addition of a methyl group to either an adenine or a cytosine, which can change the activity of the DNA segment (e.g. repression of gene transcription when methylation occurs in a gene promoter). Epigenetic variation can also play an important role in population adaptation to changing environments (Rey et al., 2016). Some epigenetic modifications are labile and reversible within an individual's lifetime, leading to phenotypic plasticity (Angers et al., 2010; Rey et al., 2016). In contrast, selection on heritable epigenetic modifications can have a role similar to that of genetic variation, albeit on a shorter time scale as a result of their higher mutation rate and instability (Angers et al., 2010; Berger et al., 2009; Danchin et al., 2018; Jablonka and Raz, 2009; Rey et al., 2016). Therefore, epigenetic variation can act as a source of heritable variation, allowing populations to adapt to changing environments more rapidly.

Epigenetic variation is influenced by both the genetic background and the environment (Feil and Fraga, 2012; Feinberg and Irizarry, 2010; Herrera et al., 2016; Richards, 2006). During mitosis and sometimes meiosis, genetic alleles are transmitted with their own determined epigenetic states (Jablonka and Raz, 2009; Richards, 2006). Epigenetic marks are also partially determined by the genotype, as the molecules needed to carry out epigenetic modifications are genetically encoded (Rey et al., 2020). Therefore, genetic and epigenetic variation may be linked in natural populations, with the two diversity facets co-varying spatially across populations (Herrera and Bazaga, 2010; Herrera et al., 2016). Alternatively, genetic and epigenetic variation could be linked as a consequence of being affected by the same neutral processes, such as genetic and epigenetic drift, mutations and gene flow. As a result, even though they are physically independent, they could still co-vary spatially (Fargeot et al., 2021; Herrera and Bazaga, 2010; Liu et al., 2018; Zhang et al., 2018). Joint investigations of genetic and epigenetic diversity have shown that there can be some correlation between genetic and epigenetic variation in natural populations because of this possible genetic influence on epigenetics (Fargeot et al., 2021; Herrera and Bazaga, 2010; Liu et al., 2012, 2018; Zhang et al., 2018; Angers et al., 2010; Rey et al., 2016).

Environmental factors such as contaminants, nutrition and parental behaviour have also been shown to affect epigenetic

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marks (Anway et al., 2005; Curley et al., 2008; Feil and Fraga, 2012; Norouzitallab et al., 2019). For instance, Yu et al. (2013) found that abiotic stresses, including warming and nitrogen addition, altered DNA methylation patterns in *Leymus chinensis*, potentially leading to epigenetic differentiation between populations. Such environmental influences on epigenetics can enable phenotypic plasticity in predictable environments or a bet-hedging strategy in unpredictable environments (Leung et al., 2016; Marsh and Pasqualone, 2014; Nicotra et al., 2015). Moreover, epigenetic variation can compensate for low genetic variation in populations by contributing to phenotypic diversity (Latzel et al., 2013; Schrey et al., 2012). This is particularly relevant for clonal species (Vogt, 2017), species with high rates of gene flow, and populations that have experienced inbreeding, bottlenecks or founder effects, such as those found in invasive species (Liu et al., 2018; Schrey et al., 2012; Sheldon et al., 2018; Vogt, 2017). Therefore, epigenetic variation in a population may be higher than genetic variation as a result of its sensitivity to the environment and the high mutation rate of epigenetic modifications (Klironomos et al., 2013; Rey et al., 2016), indicating its potential role in adaptation to changing environments.

Lira-Medeiros et al. (2010) conducted one of the first studies aimed at quantifying natural epigenetic variation in wild plant populations. Focusing on methylation marks, they were able to show that DNA methylation differentiation was higher than genetic differentiation between two populations of *Laguncularia racemosa* (a leadwood tree) in contrasting habitats, suggesting that epigenetics may be influenced by environmental conditions. Since then, there have been many more studies that have compared genetic differentiation and epigenetic differentiation in a common set of populations, and that have determined the strength of the relationship between genetic and epigenetic differentiation (i.e. spatial covariation between genetic and epigenetic differentiation: Foust et al., 2016; Johnson and Kelly, 2020; Schulz et al., 2014; Zhang et al., 2018). Herrera et al. (2016) provided a preliminary synthesis of published papers comparing the spatial structure of genetic and epigenetic differentiation between populations from eight plant species. They showed that the global level of epigenetic differentiation between conspecific populations was often higher than that of genetic differentiation. This result is important as it supports the previously mentioned concept that epigenetic variation may be under partial genetic control and may also be influenced by changes in the environment. Despite this, there are no studies that have completed an extensive meta-analysis to examine the dependency (or the semi-dependency or, conversely, the autonomy; Richards, 2006) of epigenetics on genetic variation across a number of plant and animal species. Nonetheless, given the potential of epigenetic marks for species adaptation and for informing local management and conservation plans (Rey et al., 2020), it is now crucial to produce a comprehensive and quantitative synthesis across a range of species including both plants and animals (Gurevitch et al., 2018).

Our main objective was to investigate the relationship between epigenetic and genetic differentiation in wild animal and plant populations, and to evaluate the hypothesis that epigenetic variation is independent of genetic variation. To achieve this goal, we conducted a meta-analysis of published datasets that had measured both genetic and epigenetic differentiation in the same set of plant and animal populations. We focused on methylation marks as, to date, they are the most studied type of epigenetic variation in non-model organisms. Our first aim was to test whether there was a general correlation between pairwise genetic and epigenetic differentiation across population pairs. A lack of correlation would suggest that epigenetic variation is influenced by factors other than genetic variation, such as environmental variation. However, as epigenetic variation is partially determined by genetics (Richards, 2006), we expected to find a significant and positive correlation between pairwise genetic and epigenetic differentiation across both plant and animal species. We also predicted that population pairs with low levels of genetic differentiation (e.g. invading species, populations connected by high gene flow) would exhibit a weaker correlation between genetic and epigenetic differentiation, as these populations may rely more heavily on epigenetic variation to adapt to local environmental conditions (Meröndun et al., 2019). Our second aim was to compare the global levels of genetic and epigenetic differentiation across all the datasets and examine how they differ between plant and animal species. It is expected that the level of epigenetic differentiation will be higher than that of genetic differentiation because of the influence of environmental factors on epigenetics and the higher mutation rate in epigenetic marks (Foust et al., 2016; Klironomos et al., 2013). If the level of genetic differentiation is similar to that of epigenetic differentiation, this suggests that epigenetic variation is primarily determined by genetics rather than the environment. For both the pairwise and global level of differentiation, we additionally tested whether patterns were similar or not among taxonomic groups (animals versus plants). We expected differences between taxonomic groups as, for instance, the level of epigenetic differentiation should be greater in plants than in animals as a result of the greater reliance of plants on epigenetic modifications for beneficial adaptations in changing environments (Hu and Barrett, 2017; Richards, 2011).

Review protocol

Literature search

We focused on published studies that had quantified genetic and epigenetic differentiation in the same set of plant and animal populations. Searches were undertaken in October 2020 using Web of Science, Google Scholar and PubMed to obtain papers. The keywords used in these searches were ‘epigenetic and genetic differentiation’, ‘epigenetic and genetic spatial variation’, ‘epigenetic and genetic structure’, ‘epigenetic and genetic correlation’, ‘MSAP, MS-AFLP’, ‘DNA methylation pattern and genetics’ and ‘epigenetic and genetic diversity’. Papers were initially chosen based on their titles and abstracts only. The resulting papers were further filtered and retained if they provided explicit values for the global levels of population genetic and epigenetic differentiation over all sampled populations (either directly or from analysis of molecular variance, AMOVA), and/or the correlation coefficient between pairwise genetic and epigenetic differentiation, usually in the form of Mantel tests. We also checked the reference list of each study to ensure that no other studies were missed. Each study was recorded, taking into account the authors, title, year of publication, type of phyla (plant or animal), the Latin species name, the number of sampled populations, the genetic marker used to measure genetic and epigenetic differentiation (AFLP, MSAP, microsatellites, SNPs, etc.), and the genetic and epigenetic differentiation values. The metrics used to assess genetic and epigenetic differentiation (e.g. F_{ST}, G_{ST} and ϕ_{ST}) were noted and when more than one metric was used for the same dataset, we reported all possible values.

Estimation of effect sizes from published statistics

To estimate the strength of the correlation between pairwise genetic and epigenetic differentiation, Fisher’s *Z*-transformation (Zr) was applied to each correlation coefficient to produce a standardised

effect size (Nakagawa and Cuthill, 2007). Positive Zr values mean that there is a positive correlation and vice versa, and the higher the absolute value of Zr, the stronger the correlation between pairwise genetic and epigenetic differentiation. For each effect size, the asymptotic variance (v_z) was calculated using the formula: $v_z=(n-3)$ where n is the number of sampled populations (Nakagawa and Cuthill, 2007). To compare the global levels of genetic and epigenetic differentiation for each population, the log-transformed response ratio (lnRR) was used for the standardised effect size (Mazé-Guilmo et al., 2016). lnRR was calculated, for each case study, as the natural logarithm of the global level of genetic differentiation over the global level of epigenetic differentiation. Positive lnRR values indicate that the global level of genetic differentiation is higher than the global level of epigenetic differentiation, whereas negative values indicate the opposite. The stronger the absolute value of lnRR, the higher the difference between global genetic and epigenetic differentiation. Variance of each lnRR value was calculated using the formula: $\text{Var}=[(N-2)\times K]^{1/2}$, where N is the number of populations sampled and K is the number of individuals sampled in the target population.

Quantitative synthesis of effect sizes through meta-regressions

We first assessed the strength and significance of the mean effect size (MES, i.e. mean effect size across all case studies) for Zr by running an intercept-only linear mixed model ('lmer' function from the *lme4* R package), with Zr as the response variable, and paper identity and the type of molecular marker used to estimate genetic diversity as two independent random factors. The first random term allowed us to take into account the fact that several genetic and/or epigenetic estimates are sometimes available for a single case study (e.g. when several indices of differentiation have been used). The second random term allowed us to take into account the different intrinsic characteristics of the molecular markers used to estimate genetic differentiation (Mazé-Guilmo et al., 2016). Finally, the inverse of asymptotic variance (v_z) was included in the model as the weighting parameter. This permits providing further weight to studies with a higher sample size as they are expected to provide more precise estimates. This model was used to estimate the MES for Zr and its associated 95% confidence interval (CI). To compare the strength of the correlation between plants and animals, the same model was run, but organism type (plant or animal) was added as a fixed categorical factor. Finally, a model including the global level of genetic differentiation for each case study as a fixed continuous factor (while removing organism type as a fixed effect) was used to test the hypothesis that a weaker correlation between pairwise genetic and epigenetic differentiation will be observed in species with lower levels of genetic differentiation. We therefore expected a positive relationship between Zr and the global level of genetic differentiation. To compare the global levels of genetic and epigenetic differentiation, the same three models previously described were used, except that lnRR was used as the response variable and the inverse of the variance (Var) as the weighting parameter.

Assessing for potential publication bias

We tested for potential publication bias by combining Egger's regressions and funnel plots (Egger et al., 1997; Raffard et al., 2019). Egger's regressions test the relationship between the effect size and the precision of the measure; the intercept and the slope of this relationship are expected not to differ significantly from zero if there is no publication bias. Here, we specifically ran generalized linear models (GLMs) linking the residuals of the intercept-only linear mixed model for Zr and lnRR, respectively, to the inverse of their respective variances (as a measure of precision). Funnel plots were simple scatterplots linking the residuals described above and the inverse of their respective variances. Unbiased datasets are expected to produce symmetric funnel plots (data are scattered to each part of the distribution) with less variance in effect sizes for studies with large sample sizes and more variance in effect sizes for studies with small sample sizes (Raffard et al., 2019).

Literature overview

The review process resulted in the final selection of 53 papers, amongst which were 34 papers that were used to test for the correlation between pairwise genetic and epigenetic differentiation and 43 papers that were used to compare the global levels of genetic and epigenetic differentiation (see Fig. 1 and Supplementary Materials and Methods). This quantitative review encompassed 32 species (23 plant and 9 animal species, which resulted in 71 effect sizes) for the correlation between pairwise genetic and epigenetic differentiation, and 39 species (30 plant and 9 animal species, which resulted in 91 effect sizes) to compare the global levels of genetic and epigenetic differentiation. There was a strong bias toward plant species in both cases, which probably reflects the fact that epigenetic studies in the wild have emerged from plant biologists.

Is there a general correlation between pairwise genetic and epigenetic differentiation?

The MES for the correlations between pairwise genetic and epigenetic differentiation was positive and significantly different from zero (Zr_{global}=0.490, 95% CI=0.249–0.831; Fig. 2A). This indicates that, across all of the datasets, pairwise epigenetic differentiation was positively correlated with pairwise genetic differentiation in the same set of populations, suggesting that they spatially covary with one another. We did not find a significant difference between the MES estimated for animals and that for plants (F=0.236, d.f.=1, 23.908, P=0.632; Zr_{animal}=0.408, 95% CI=−0.060−0.876, Zr_{plant}=0.535, 95% CI=0.035–1.035; Fig. 2B).

We further found a positive and significant relationship between Zr and the global level of genetic differentiation of populations (F=6.370, d.f.=1, 19.378, P=0.024), indicating that – as expected – the association between pairwise genetic and epigenetic differentiation was on average weaker when measured between pairs of populations that were weakly differentiated genetically (Fig. 3).

Are the global levels of genetic and epigenetic differentiation similar in effect size?

The MES of the global level of genetic and epigenetic differentiation was positive and significantly different from zero

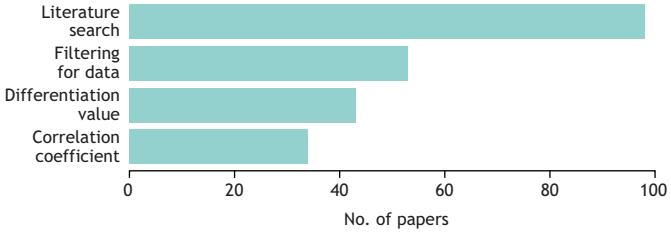

Fig. 1. Filtering steps of the meta-analysis. Of the 98 scientific papers retrieved from the search, 53 were conserved after filtering for data availability, among which 43 were used for comparing global levels of genetic and epigenetic differentiation and 34 were used for estimating correlation between pairwise estimates of genetic and epigenetic differentiation.

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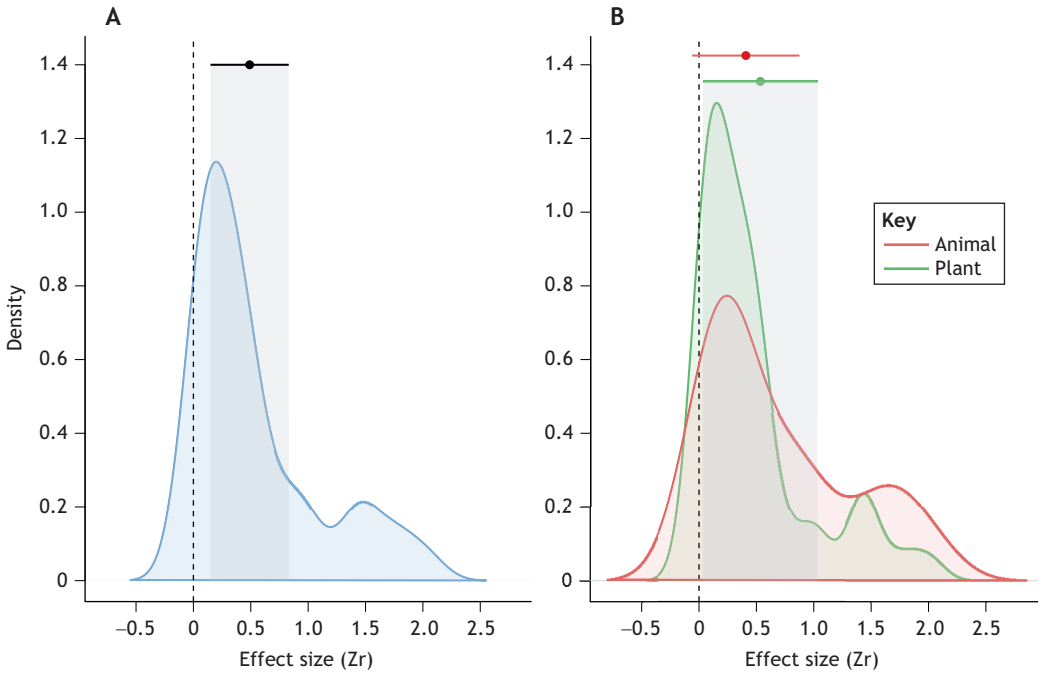

Fig. 2. Density plots generated from meta-analyses depicting the distribution of effect sizes estimated from the correlation between genetic and epigenetic pairwise differentiation. (A) Global distribution of effect sizes (Zr) across plants and animals. (B) Distribution of effect sizes for animals and plants separately. A positive value indicates a positive correlation between genetic and epigenetic pairwise differentiation, while a negative value indicates a negative correlation. The circles represent the mean effect sizes (MES) across all case studies and horizontal lines are the 95% confidence intervals.

($lnRR_{global}$=0.416, 95% CI=0.028–0.803; Fig. 4A). This means that, across all datasets, populations were generally more genetically differentiated from one another than epigenetically differentiated. We did not find a significant difference between the effect size measured for plants and that for animals, although there was a tendency toward a lower MES in animals than in plants (F=0.852, d.f.=1, 4.282, P=0.405; $lnRR_{animal}$=−0.099, 95% CI=−1.081–0.884, $lnRR_{plant}$=0.510, 95% CI=−0.558–1.579; Fig. 4B).

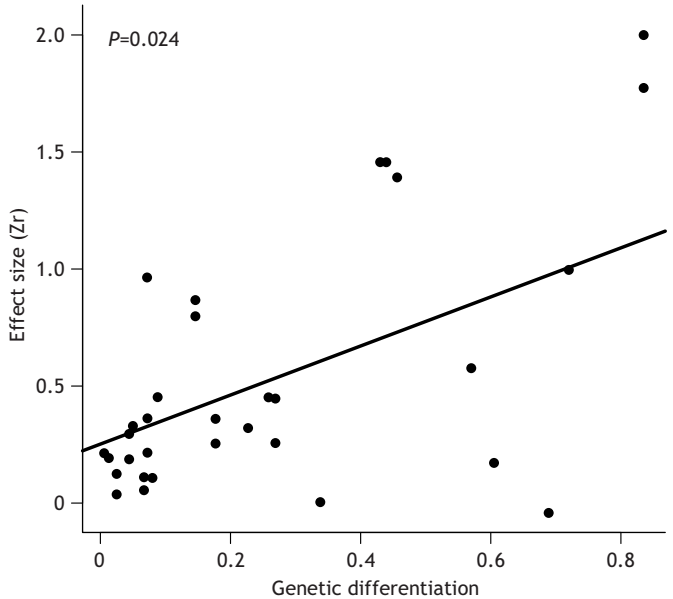

Fig. 3. Biplot illustrating the relationship between pairwise genetic and epigenetic differentiation (Zr) and genetic differentiation between population pairs. The P-value is indicated (where significance was set at α=0.05).

We did not find a significant relationship between lnRR and the global level of genetic differentiation of populations (F=1.135, d.f.=1, 18.984, P=0.301), indicating that the global level of epigenetic differentiation among populations was not necessarily higher than the global level of genetic differentiation among populations when populations were weakly differentiated genetically (Fig. 5). However, lnRR estimates were much more dispersed for sets of populations that were weakly differentiated genetically; epigenetic differentiation tended to be higher than genetic differentiation for half of the cases (lnRR<0) and genetic differentiation tended to be higher than epigenetic differentiation for the other half (lnRR>0). In contrast, when genetic differentiation among the set of populations was high, epigenetic and genetic differentiation were of similar amplitude (lnRR≅0; Fig. 5).

Evidence for publication bias

Eggers' regressions identified potential bias for Zr, but not for lnRR. Indeed, both the intercept and the slope differed significantly from zero for Zr (α=−0.376, t=−4.934, P<0.001; β=0.446, t=4.159, P<0.001), whereas for lnRR, only the intercept differed significantly from zero (α=−0.526, t=−2472, P=0.015; β=0.631, t=1.828, P=0.071). Nonetheless, for both Zr and lnRR, the intercept was negative, indicating that there was no publication bias toward high and significant values. Regarding the slope of the Eggers's regression for Zr, inspection of the funnel plot (Fig. 6A) indicates that the positive slope was mainly driven by a few negative values with a low precision (lower left-hand part of the plot) and not by an excess of highly positive values. Moreover, the funnel plots for both Zr and lnRR (Fig. 6A,B) revealed effect size values that were relatively well symmetrically scattered within the plot, which suggests that any bias – if it exists – is weak.

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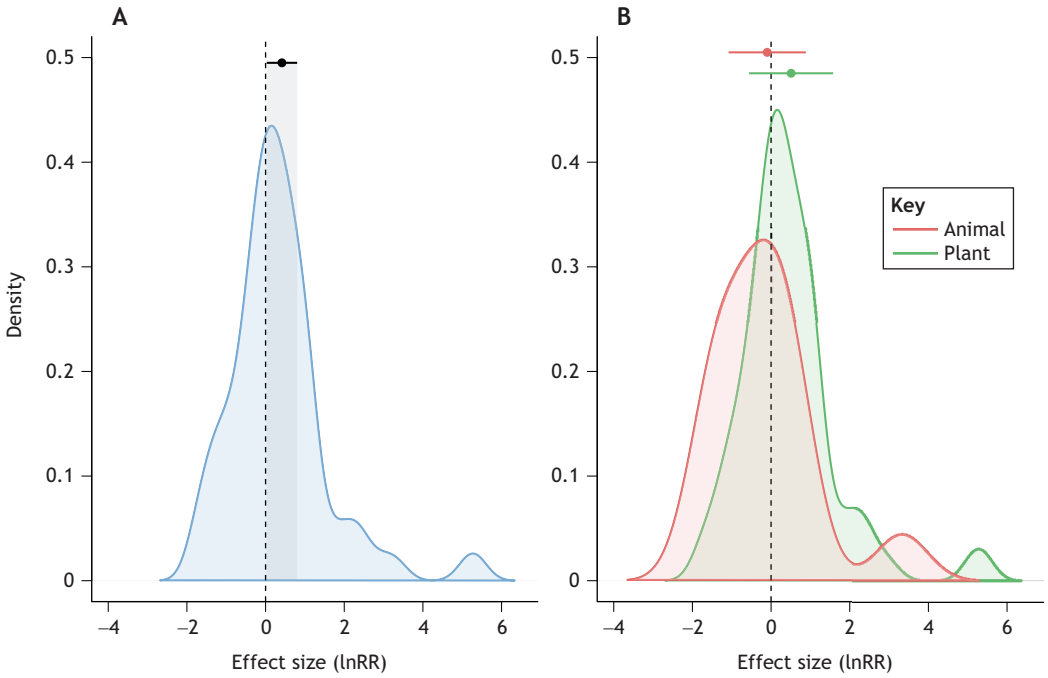

Fig. 4. Density plots generated from meta-analyses depicting the distribution of effect sizes comparing global levels of genetic differentiation with epigenetic differentiation. (A) The global distribution of effect sizes across both plants and animals (log-transformed response ratio, lnRR). (B) The distribution of effect sizes for animals and plants separately. A positive value indicates that the level of genetic differentiation is higher than the level of epigenetic differentiation, while a negative value indicates the opposite. The circles represent the mean effect sizes (MES) across all case studies, and the horizontal lines indicate the 95% confidence intervals.

Discussion

Pairwise genetic and epigenetic differentiation co-vary spatially

We found a significant and positive correlation between pairwise estimates of genetic and epigenetic differentiation that holds true for both plants and animals. This means that as genetic differentiation increases between pairs of populations, epigenetic differentiation also increases. This indicates that (i) spatial congruency exists between the genetic and epigenetic structure of populations and (ii) the two markers are not completely independent from each other. This was expected given the partial genetic control of epigenetic variation, resulting from a partial epigenetic determinism by genotype (Richards, 2006; Richards et al., 2017; Snell-Rood et al., 2013). Another alternative – yet non-mutually exclusive – hypothesis is that genetic and epigenetic variation change in parallel

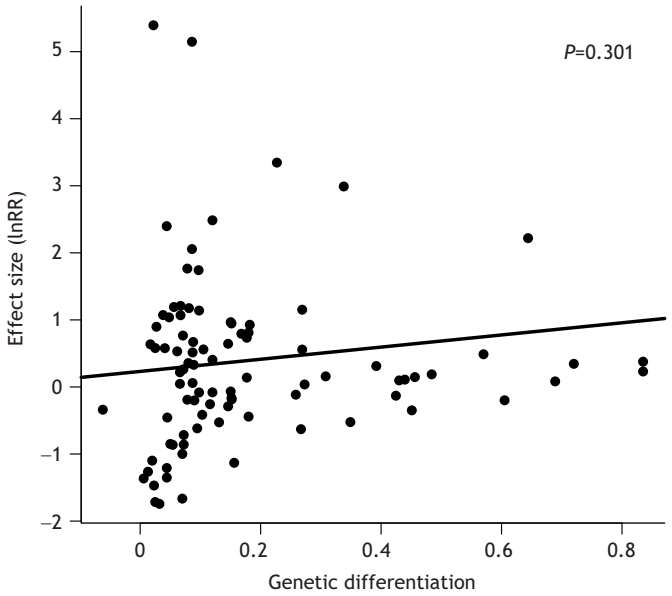

Fig. 5. Biplot illustrating the relationship between the global level of genetic and epigenetic differentiation (lnRR) and genetic differentiation among populations. The *P*-value is indicated (where significance was set at α=0.05).

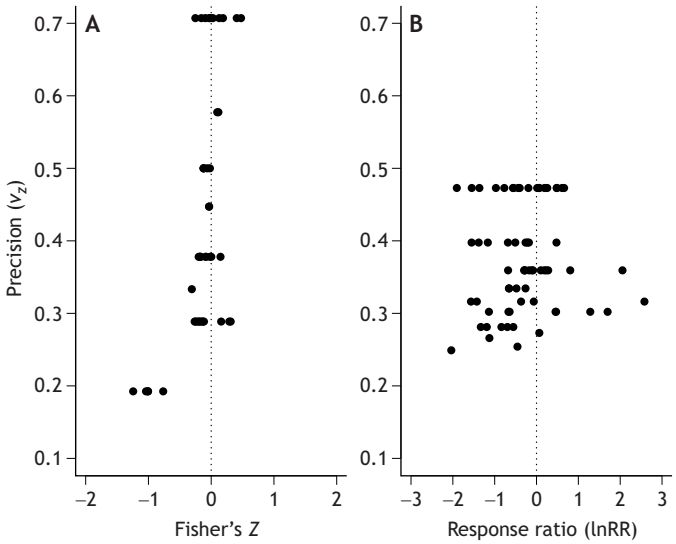

Fig. 6. Funnel plots showing the distribution of effect sizes in relation to precision. (A) Effect sizes of pairwise genetic and epigenetic differentiation (Zr). (B) Effect sizes of the global level of genetic and epigenetic differentiation (lnRR).

(and are hence related) with one another as a result of the common influence of neutral processes, such as random drift, mutations and the effective dispersal of individuals (Herrera and Bazaga, 2010; Zhang et al., 2018). It is extremely difficult to tease apart these two mechanisms (genetic determinism versus common neutral processes acting on markers) from empirical patterns. Yet, we argue that this might be achievable, for instance by estimating proxies for neutral processes (e.g. Dauphin et al., 2023; Manel and Holderegger, 2013; Prunier et al., 2017) and for estimating genetic relatedness among individuals (e.g. Maze-Guilmo et al., 2014), and taking this information into account in causal models (Fourtune et al., 2018) to reveal likely mechanisms sustaining the link between genetic and epigenetic differentiation.

Global levels of genetic and epigenetic differentiation also co-vary spatially

Regarding the global levels of genetic and epigenetic differentiation, we expected a higher level of epigenetic differentiation than genetic differentiation across all the datasets, mostly because of the expected influence of environmental factors on epigenetics and the higher mutation rate in epigenetic marks (Foust et al., 2016). However, we failed to verify this prediction and instead we found evidence that global levels of genetic differentiation were slightly higher than (or at least similar to) levels of epigenetic differentiation. This suggests that, overall, genetic markers tended to be more informative than epigenetic markers for inferring the spatial structure of populations, which holds true for plants and animals. This finding, although not expected across all case studies, is coherent with some local scale studies. For instance, Schulz et al. (2014) investigated epigenetic variation in relation to habitat conditions in populations of *Viola elatior* and found that genetic differentiation was higher compared with epigenetic differentiation. They further showed that epigenetic variation was correlated with habitat conditions and that reduced epigenetic variation in *V. elatior* populations was probably due to similar habitat conditions. It is unlikely that our general pattern (genetic differentiation is higher than epigenetic differentiation) can be explained by a lack of dissimilarity among habitat conditions investigated by researchers, as is the case for Schulz et al. (2014). Rather, it is possible that genetic variation could have a strong influence on epigenetic variation and/or that the local environment has a limited influence on epigenetic variation (Richards, 2006). We hypothesize that the impact of the environment on epigenetic marks might actually be more subtle (or labile) than the influence of neutral processes on the spatial distribution of epigenetic diversity, and this environmental dependency might be blurred by other processes when epigenetic population structure is inferred at the 'genome-wide' level. If this hypothesis is true, we argue that future studies should instead be focused at the local genomic scale by isolating (either *a priori* or *a posteriori*) the few loci within the genome that are likely to be more strongly affected by the environment than by neutral processes. This shift from 'genome-wide' to 'local genomic scale' studies will be made possible with the increasing availability of targeted (epi-)genomic tools (e.g. Laine et al., 2023; Nabais et al., 2023).

Important details are hidden behind the general patterns

As discussed above, the two general patterns we highlighted above suggest that, overall, epigenetic variation is not independent from genetic variation, as expected (Richards, 2006). This non-independence between genetic and epigenetic markers may have been due to methodological bias, especially when the same restriction enzyme (MspI) is used to infer both genetic and epigenetic variation (Schulz et al., 2013). However, such cases were relatively rare in our meta-analysis, and when removed from the meta-regression, the main conclusions remained unchanged (after data exclusion: Zr_{global}=0.474, 95% CI=0.275–0.669, $lnRR_{global}$=0.442, 95% CI=0.008–0.875), making it unlikely that methodological artifacts explain our results. That explanation being excluded, we further revealed interesting patterns when considering the relationships between each effect size and the genetic differentiation of populations, for both the correlation between genetic and epigenetic pairwise differentiation and the comparison of global levels of genetic and epigenetic differentiation. We found that for populations that were weakly differentiated genetically, the correlation between genetic and epigenetic pairwise differentiation was weak (close to zero) and that the ratio of the global levels of genetic and epigenetic differentiation was highly heterogeneous (half of the values were positive, half were negative). For the ratio of the global levels of genetic and epigenetic differentiation, this might indicate that in some cases (positive values), epigenetic variation leads to an ecological convergence of populations (because habitat conditions are similar, as in Schulz et al., 2014), and in some cases (negative values), it leads to an ecological divergence of populations (because habitat conditions are dissimilar, Rey et al., 2020). Weak genetic differentiation among populations can arise because of the recent divergence of populations, the recent invasion/colonisation of some populations and/or a non-negligible amount of effective dispersal [leading to (epi-)gene flow] among populations. In these specific cases, our meta-analysis provides evidence that epigenetic marks are (partly) independent from genetic marks. This pattern is expected as epigenetic marks have been found to be particularly relevant for species adaptation when populations lack genetic variation (e.g. Feiner et al., 2022; Sheldon et al., 2018), which is particularly obvious in clonal species (Rey et al., 2020; Vogt, 2017, 2022). Our global synthesis of published papers therefore confirms the idea that epigenetic marks might be particularly important for the rapid adaptation of species colonising new environments (priming effect of epigenetic marks leading to assimilation; Danchin et al., 2018; Rey et al., 2016) and for informing the ecological structure of these populations, which can obviously be poorly revealed from genomic information (Rey et al., 2020).

And, after all, plants and animals are not that different

Finally, we predicted that the level of epigenetic differentiation would be higher in plants than in animals, but this was not verified. Both groups were not significantly different from zero, meaning that the levels of genetic and epigenetic differentiation were similar to each other within plants and animals individually. Both groups were also not significantly different from each other, meaning that they had similar levels of genetic and epigenetic differentiation. There was also no difference regarding the strength of the correlations between pairwise estimates of genetic and epigenetic differentiation. This could be due to the overall similarity of epigenetic mechanisms in plants and animals, particularly mammals (Pikaard and Mittelsten Scheid, 2014), or to the poor representation of animal species in our meta-analysis. If we assume that this finding has a biological basis, we can speculate that because animals are often more mobile than plants, they are exposed to a greater range of environmental conditions and differences in habitats. Consequently, epigenetic marks in animals may adaptively permit organisms to cope with this sudden variation (Johnson and Kelly, 2020; Massicotte and Angers, 2012; Meröndun et al., 2019; Wogan et al., 2020). In contrast, plants are often more

sessile and may be limited genetically for adapting to the local environment; epigenetic marks may therefore be important in these cases (Hu and Barrett, 2017; Richards, 2011). Given the broad nature of the meta-analysis, these conclusions would require more specific analyses to be confirmed, and for instance additional factors specific to each study should be taken into account, such as the state of the population (natural, common garden, *in vitro*) and habitat heterogeneity, but also species characteristics that are likely to influence the temporal and spatial dynamics of genetic and epigenetic marks (population history, dispersal ability, reproductive mode, age at maturity, etc.). Despite this limit, our results suggest that epigenetic variation can be important for both plants and animals, which broadens the adaptive relevance of non-genetic processes of adaptation.

Some evident limitations

Meta-analyses in an ecological context are often complicated and can be associated with problems, such as heterogeneity, the over- or under-representation of species in the literature, the absence of certain evidence and publication bias (Gurevitch et al., 2018; Nakagawa and Santos, 2012). For instance, and as stated above, our meta-analysis is obviously biased towards studies on plant species, which reflects a scientific reality. As we found similar patterns for plants and animals, we encourage researchers to further investigate the genetic and epigenetic structures of wild animal populations as this could provide relevant sources. More generally, we encourage plant and animal biologists to integrate additional co-factors (e.g. local habitat conditions, pairwise relatedness, proxies of drift such as population size, species characteristics, etc.) and to integrate information both at the genomic level and at the loci level in the analysis of the genetic–epigenetic structure of wild populations, which should permit testing of proper *a priori* hypotheses and provide insights into the mechanistic links between genetic and epigenetic markers (e.g. Fargeot et al., 2021; Fourtune et al., 2018; Snell-Rood et al., 2013). As briefly mentioned above, next-generation sequencing (NGS) may be particularly useful to generate novel mechanistic insights into the relationships between genetic variation, epigenetic marks and the environment. Recent methodological reviews (e.g. Laine et al., 2023) provide relevant guidelines for ecologists, and recent empirical studies (e.g. Mounger et al., 2022; Meröndun et al., 2019; Gao et al., 2021) nicely illustrate the steps that can be skipped by adopting NGS approaches at the genome-wide level. For instance, by focusing on genetic and epigenetic variation at the scale of DNA sequence fragment, Mounger et al. (2022) were able to isolate the effects of population identity and habitat type (and their interactive effect) on epigenetic variation, while controlling for DNA variation. By providing access to the sequences of DNA fragments, their position in the genome and their potential functional roles, it is obvious that NGS approaches will change and enlarge our vision of the role of epigenetic (and genetic) variation for population evolution.

Synthesis and conclusions

We found strong evidence that genetic variation and methylation marks are not independent from one another as (i) pairwise estimates of genetic and epigenetic differentiation were related with one another and (ii) on average, global estimates of genetic and epigenetic differentiation were of similar amplitude. This suggests that revealing the epigenetic structure of wild populations independently from their genetic structure is not trivial, and that the two markers share some information. Nonetheless, when populations were weakly differentiated genetically (i.e. when they share a common genetic ancestry), we found evidence that the association between genetic and epigenetic markers was weaker, which suggests that epigenetic information might – as expected – be particularly relevant in these cases.

Epigenetic marks are an important non-genetic component for the rapid adaptation of organisms to changing environments (Danchin et al., 2011; Jablonka and Raz, 2009; Rey et al., 2016). More recently, it has been proposed that epigenetic marks could be a useful piece of information for improving the management and conservation of wild populations (Rey et al., 2020). An important premise for conservation epigenetics to be relevant is that epigenetic marks provide information that is non-redundant from genetic information, especially regarding the spatial structure of populations. Here, we show evidence that, overall, genetic variation probably plays a large role in determining a specific type of epigenetic variation (methylation variation) in wild populations. Although underlying mechanisms as well as patterns for other types of epigenetic marks (histone modification, non-coding RNA) are still to be revealed, this implies that the epigenetic structure of wild populations cannot be interpreted without taking into account their genetic structure (Fargeot et al., 2021; Herrera et al., 2016). Moreover, we demonstrated that the genetic–epigenetic linkage was weaker for sets of populations that were weakly differentiated genetically, supporting the hypothesis that methylation markers might be particularly relevant in these specific cases for revealing the local and contemporary adaptation of populations (Rey et al., 2020). We stress the importance of increasing the number of case studies from wild populations and focusing on other types of epigenetic marks so as to better grasp the mechanisms sustaining the genetic–epigenetic linkage, which is achievable by investigating the genetic and epigenetic co-structure of wild populations at different spatial scales, and by jointly informing the landscape features that may impact key evolutionary processes (drift, dispersal, mutation, selection), i.e. by moving towards a landscape epigenetics perspective (Dauphin et al., 2023).

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