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Harnessing the power of multi-omics data for predicting climate change response

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Abstract

1. Predicting how species will respond to future climate change is of central importance in the midst of the global biodiversity crisis, and recent work has demonstrated the utility of population genomics for improving these predictions.
2. Here, we suggest a broadening of the approach to include other types of genomic variants that play an important role in adaptation, like structural (e.g. copy number

variants) and epigenetic variants (e.g. DNA methylation). These data could provide additional power for forecasting response, especially in weakly structured or panmictic species.

3. Incorporating structural and epigenetic variation into estimates of climate change vulnerability, or maladaptation, may not only improve prediction power but also provide insight into the molecular mechanisms underpinning species' response to climate change.

Keywords: forecasting, genomic offset, structural variation, epigenetic variation, panmixia

1. *Current methods of predicting future climate change response*

The rapid loss of biodiversity on a global scale calls for efforts to revolutionise our ability to predict and mitigate this loss. Ecological niche modelling, or species distribution models (SDMs), remains a powerful approach for predicting distributional shifts (Jarvie & Svenning 2018), especially with the integration of genetic data (Stanley et al. 2019). However, recent work has highlighted a need to more explicitly integrate information about evolutionary adaptation to provide holistic predictions of biodiversity response to climate change (Collela et al. 2020; Razgour et al. 2019). This is especially relevant since evolutionary adaptation is critical for species response to environmental stress, particularly when shifts in range limits and ontology are outpaced by climate change. Several recent papers employ a combined population genomics and gradient forest modelling approach to predict climate maladaptation by estimating genetic (genomic) offset or genomic vulnerability (e.g. Bay et al. 2018; Fitzpatrick & Keller 2015; Layton et al. 2021)- a metric defined as the mismatch between current and future genetic variation. The method has gained popularity in recent years for use in vertebrates and plants (Figure 1), largely because it brings an evolutionary perspective into the work that explicitly considers the adaptive capacity of populations to respond to change (Fitzpatrick & Keller 2015). This method has recently been supported by experimental work where populations of balsam poplar (*Populus balsamifera L.*) with a larger genomic offset performed worse in a common garden experiment (Fitzpatrick et al. 2021), in line with recent calls for efforts to validate these predictions (Capblancq et al. 2020).

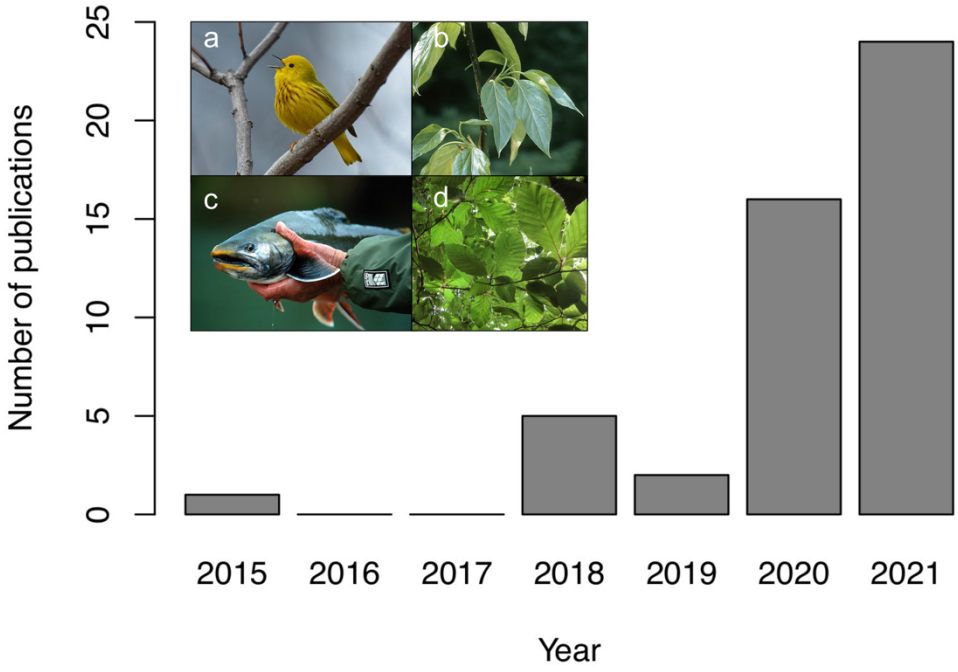

Figure 1. Number of publications that mention genetic offset, genomic offset or genomic vulnerability in the fields of ecology and evolutionary biology (Supplementary File 1). Data was retrieved through a literature search in Ex Libris Primo using the search string: "genetic offset" OR "genomic offset" OR "genomic vulnerability". Inset: a selection of taxa for which genomic offset has been calculated- a) yellow warbler (*Setophaga petechia*), b) balsam poplar (*Populus balsamifera*), c) Arctic Charr (*Salvelinus alpinus*), and d) European beech (*Fagus sylvatica*). Results of the literature search are available in Supplementary File 2. Images derive from Wikimedia Commons and license details are available in Supplementary File 3.

Ultimately, the genomic basis of adaptation encompasses a variety of types of genomic variation. To date, these methods have largely examined single nucleotide polymorphisms (SNPs), identifying environmentally associated SNPs through genotype-environment association (GEA) analyses and using these to predict future response. Genome-wide SNPs offer high resolution for investigating genetic diversity and population structure, for mapping genomic regions of interest and for genome-wide association studies (GWAS), including GEA (Zimmerman et al. 2020). Despite their advantages, SNP markers have a lower mutation rate than other genetic variants that may limit their power to detect and predict rapid responses to

environmental change. For example, some structural variants (i.e., CNVs) have mutation rates more than 100 times that of SNP sites (Conrad & Hurles 2007; Fu et al. 2010). Additionally, other types of genetic variants play a more important functional role in adaptation than SNPs do. For instance, through the modulation of gene expression, where changes can occur at a rate faster than DNA mutation and more comparable to climate change (Lighten et al. 2016; Dorant et al. 2020), or through reduced recombination that helps to facilitate adaptation such as in the case of chromosomal rearrangements (Guerrero et al. 2012). In fact, non-SNP variants may play an especially important role in detecting local adaptation in systems where little genetic structure has been recovered from sequence variation (Dorant et al. 2020). Because non-SNP variants provide additional information about adaptive differences, and because a variety of molecular mechanisms have been shown to play a role in adaptation (Tigano et al. 2016), there exists a need to consider other types of variants in future predictions of climate change response. Here, we discuss the importance of non-SNP variation in adaptation and we propose a workflow for incorporating this data into existing pipelines for forecasting future response to climate change. This workflow has broad utility across a variety of systems, spanning marine, terrestrial and freshwater environments, and it provides insight into the molecular mechanisms underpinning biodiversity response to climate change.

2. Non-SNP variation

2.1 Structural variation

Structural variants, including insertions, deletions and inversions, are an important source of genetic variation that have gained increased attention for their role in adaptation (Mérot et al. 2020; Quan et al. 2021). Copy number variants (CNVs), duplications and deletions in the genome that vary among individuals, have been especially critical in understanding genotype-phenotype associations (Sjödin & Jakobsson 2012; Xu et al. 2016) and these can be inherited or arise *de novo* (Thapar & Cooper 2013). The power of copy number variation for facilitating adaptation has recently been demonstrated in yeast cells, where copper exposure induced copy number amplification of copper resistant genes (Hull et al. 2017). Additionally, recent work by Dorant et al. (2020) demonstrated that CNVs provided greater resolution of genetic differentiation and

were more significantly associated with environmental variables compared to SNP markers in a GEA analysis in American lobster (*Homarus americanus*). This work employed a reduced-representation shotgun sequencing approach to identify CNVs, produce a matrix of normalised read counts for individuals and use this matrix in a redundancy analysis (RDA) to identify environmentally-associated CNV candidates (Dorant et al. 2020). Similarly, Layton et al. (2021) employed SNP signal intensities, which represent putative CNVs (Hirase et al. 2014), in a GEA and for calculating genomic offset. The general patterns of offset were similar among SNP and signal intensity datasets (Figure 2), but there were some fine-scale, regional differences that may be relevant for conservation management (Layton et al. 2021). Although CNVs are gaining attention for their role in adaptation, no study has looked to directly integrate validated CNVs into predictions of climate change response, whether that be genomic offset or future distributional shifts.

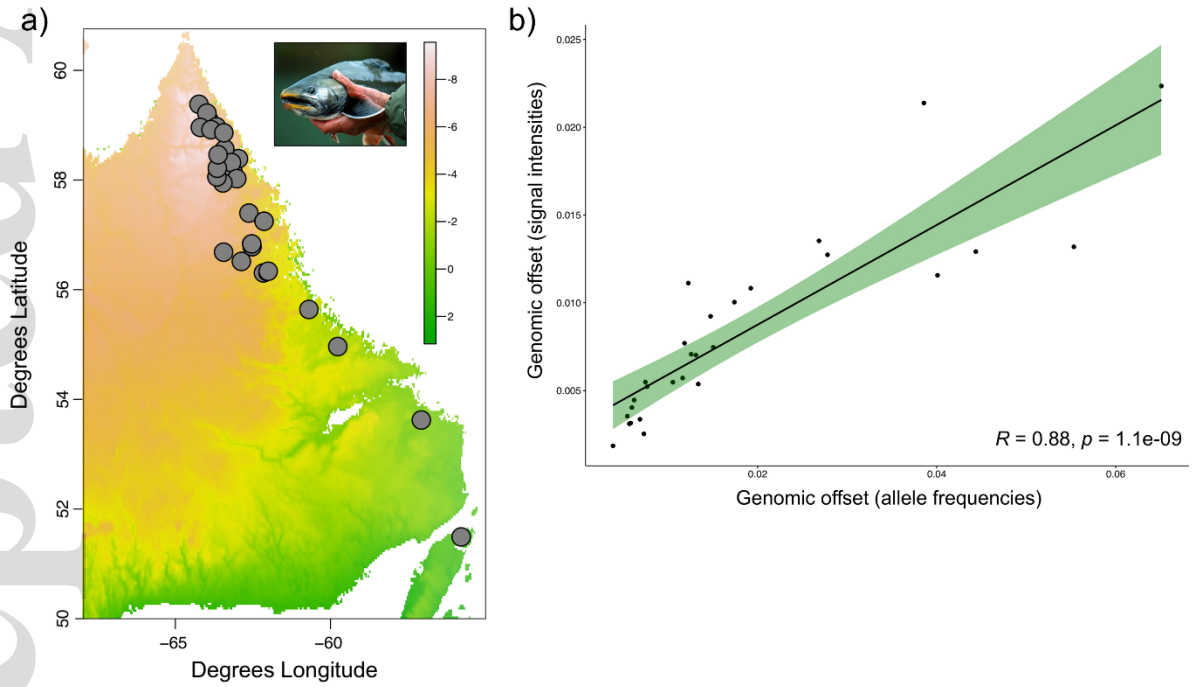

Figure 2. a) Populations of Arctic Charr (*Salvelinus alpinus*) sampled across a climate gradient in northeastern Canada displayed on a map of annual mean temperature (°C; BIO1) from WorldClim (Fick & Hijmans 2017). Charr image derives from Wikimedia Commons and license details are available in Supplementary File 3. b) The relationship between genomic offset calculated with allele frequencies (SNPs) and signal intensities (putative CNVs) for 28 populations of *S. alpinus*. Data derive from Layton et al. (2021).

Other sources of structural variation have been shown to play a role in adaptation, including chromosomal fusions and inversions (e.g. Sinclair-Waters et al. 2018; Wellband et al. 2019; Kess et al. 2020). For instance, Sinclair-Waters et al. (2018) discovered a large inverted region on LG01 in Altantic cod (*Gadus morhua*) containing several genes involved in salinity and temperature adaptation. Additionally, recent work has highlighted the importance of short structural variants (SSVs) in adaptive evolution, specifically repetitive sequences of short base pair motifs (1-6 bp) (simple sequence repeats (SSRs) or short tandem repeats (STRs)) (Reinar et al. 2021). In fact, SSRs have recently been shown to regulate gene expression in both *Arabidopsis* (Reinar et al. 2021) and penaeid shrimp (Yuan et al. 2021), with a role in driving adaptive osmoregulatory capacities during salinity stress in the latter. Given their importance in promoting adaptive evolution, these sources of variation may also have utility for genomic prediction methods.

2.2 Epigenetic variation

The role of epigenetic variation in enabling adaptation to novel environments has gained recent attention in the literature and remains contested (Richards et al. 2017; Münzbergová et al. 2018). This variation, that includes structural modification of DNA (i.e. DNA methylation), arises through epimutation or is induced environmentally (Angers et al. 2020). When environment induces epigenetic change, this change can be transmitted among generations (transgenerational inheritance) and selection on epigenetic variants can produce novel phenotypes (McGuigan et al. 2021). This process may enable a more rapid response to environmental change than genetic variation alone (Liu 2013; Kronholm & Collins 2016; Verhoeven et al. 2016; Schmid et al. 2018). However, this response may also be disrupted when parental and offspring environments show a high degree of mismatch (McGuigan et al. 2021). Nonetheless, Gugger et al. (2016) found that climate explained more of the variation in methylation patterns than in SNPs in an environmental association analysis in valley oak (*Quercus lobata*), and these methylation variants were located near genes involved in plant response to environment. Additionally, Kronholm et al. (2017) found that inhibiting epigenetic responses slowed adaptation of green algae to novel environments. As such, there is growing evidence to

suggest that epigenetic variation plays an important role in adaptation, especially in species with low genetic diversity that limits their ability to adapt to novel environments (Liebl et al. 2013).

Methylation data is typically acquired through whole genome methylation profiling (global) or targeted methylation analysis (gene-specific) using a number of possible approaches outlined in Kurdyukov & Bullock (2016). From this, epigenome-wide association studies (EWAS) have been frequently used to identify differentially methylated regions (DMRs) associated with human disease phenotypes (Imgenberg-Kreuz et al. 2016; Ruiz-Arenas & González 2017; Küpers et al. 2019), but these studies also have utility for identifying DMRs associated with the environment. In fact, Can et al. (2021) use an EWAS approach to identify methylated regions associated with complex traits in plants, including those related to fitness and adaptation. Similarly, Heckwolf et al. (2019) employ a combined genomics and methylation approach to identify DMRs across a salinity cline in three-spined stickleback (*Gasterosteus aculeatus*) populations. Furthermore, Ruiz-Arenas et al. (2017) employed a redundancy analysis (RDA) to identify DMRs, conceptually similar to the RDA employed by Layton et al. (2021) to identify environmentally-associated outlier loci in Arctic Charr (*Salvelinus alpinus*). DNA methylation mediates transgenerational plasticity (Herman & Sultan 2016) and this plasticity has been shown to be critical for organisms, like oysters, corals and fish, in responding to rapid environmental change (Parker et al. 2015; Donelson et al. 2016; Putnam & Gates 2016; Hofmann et al. 2017). The heritability of this epigenetic variation underpinning environmentally-driven plasticity needs further study, but a recent review highlights several examples of multigenerational inheritance in plants and animals exposed to environmental (extrinsic) sources of epigenetic variation (Anastasiadi et al. 2021)(Figure 3). As such, the burgeoning field of ecological epigenomics shows great promise for improving forecasts of species' responses to climate change.

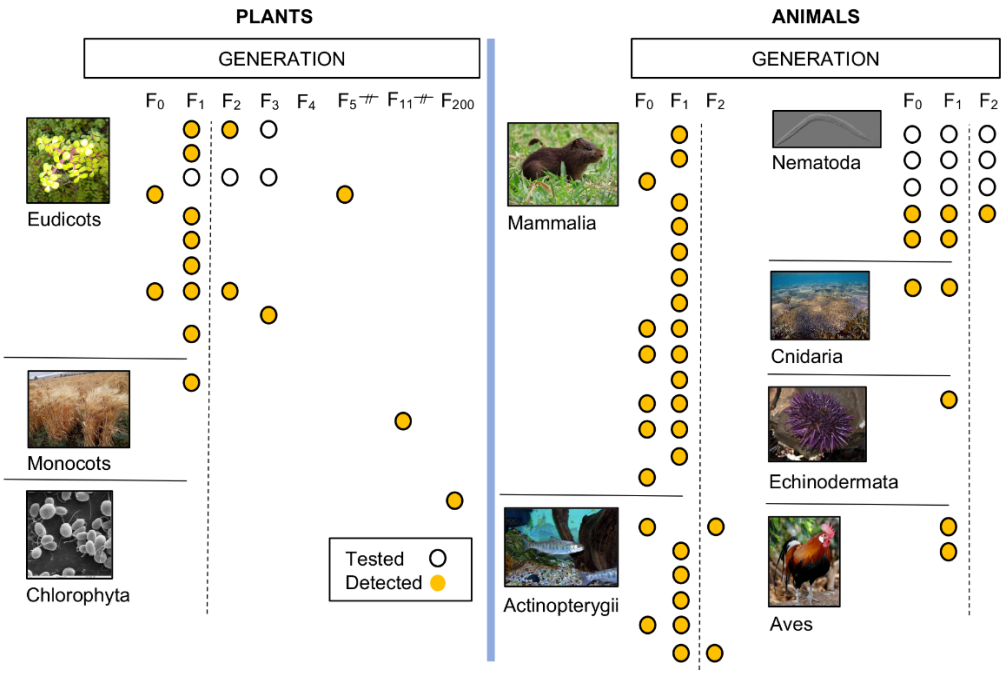

Figure 3: Patterns of transgenerational inheritance in plants and animals exposed to environmental sources of epigenetic variation. The generation in which epigenetic effects were tested is denoted by an open black circle and the generation in which the effects were detected is denoted by an orange circle. Data points to the right of vertical dashed lines indicate instances of multigenerational inheritance (>F_1). Data derive from Anastasiadi et al. (2021) and references are provided in Supplementary File 4. Images derive from Wikimedia Commons and license details are available in Supplementary File 3.

There is considerable controversy surrounding the role of epigenetic variants in adaptive evolution, some of which is focused on whether the phenotypic change driven by these variants can be inherited over multiple generations without being induced. The argument against transgenerational inheritance centres around the removal of these epigenetic marks during meiosis but recent work has shown that this removal is incomplete in some cases (e.g. Skvortsova et al. 2018) or it can be maintained through a single parent (e.g. Jiang et al. 2013). Anastasiadi et al. (2021) provide multiple examples of transgenerational inheritance across different taxa, some of which extend beyond just parental effects (Figure 3). Another criticism is the dependency of epigenetic variants on genetic variants and untangling the relationship among the two can be complex given that one type of variant can invoke change in the other (Smith &

Ritchie 2013). However, cases of truly independent epigenetic variation do exist. For instance, Gunasekara et al. (2019) demonstrated that while some methylated loci involved in human phenotypic variation were controlled by *cis*-acting variants, epigenetic variation at other loci was independent of genetic variation. Similarly, while Dubin et al. (2015) found that most epigenetic variation in *Arabidopsis* was driven by *trans*-acting loci, other studies have shown that a significant portion of phenotypic change in *Arabidopsis* is due to epimutation independent of genetic variation (Kooke et al. 2015; Schmid et al. 2018). In fact, Liu et al. (2020) suggest that much of this controversy may be due to misunderstanding and a lack of consistency across experimental systems.

3. Applying this methodology

Undoubtedly, non-SNP variation is important for adaptation and this data has utility in predictions of future climate change response. This may be especially relevant in species with large, panmictic populations, including terrestrial arthropods (e.g. Weeks et al. 2014) and many marine species (e.g. Deagle et al. 2015), where genetic variation is lacking. The pipeline presented here demonstrates best practice for incorporating non-SNP variation into predictions of climate change response using Antarctic krill, *Euphasia superba*, as an example.

The highly mobile nature and planktonic larval dispersal of many marine species, including Antarctic krill (*Euphausia superba*), often facilitates extensive gene flow with weak population structure among constituent populations. These widespread marine species are also exposed to environmental heterogeneity and differential selective pressures across their range. Deagle et al. (2015) uncovered range-wide panmixia in *E. superba* with a dataset of more than 12,000 SNPs sampled from multiple populations around Antarctica spanning thousands of kilometres (Figure 4a). This suggests that adaptive diversity is lacking in this species and is problematic since climate change is already driving habitat shifts and ontological changes in *E. superba* (Veytia et al. 2020) and krill harvesting in the region has significantly increased (Flores et al. 2012). Here, we demonstrate how copy number variants and methylation signals could be employed for forecasting future response in this vital species. First, samples should be collected across environmental gradients, in this case, across the steep east-west temperature gradient in Antarctica (Siegert et al. 2019) (Figure 4b). Because we expect to see age-related impacts on DNA

methylation (Jansen et al. 2019), specimens should be aged by counting eyestalk rings (Kilada et al. 2017). Next, response matrices comprised of either i) methylation levels of candidate DMRs, generated with whole-genome or targeted bisulfite sequencing (Kurdyukov & Bullock 2016), or ii) normalised read counts of candidate CNVs, generated with long and short-read sequencing (Chaisson et al. 2019), are used alongside environmental data in an RDA for GEA analyses (Figure 4c). Marine data layers can be readily extracted from Bio-ORACLE (Assis et al. 2017), and if applicable, additional environmental data from WorldClim (Fick & Hijmans 2017) can be used for other environments (e.g. integrating across ecosystems for taxa that use both marine and freshwater environments during their life cycle). After identifying outlier CNVs and DMRs in the redundancy analysis, the methylation levels and normalized read counts of these outliers can be used for downstream gradient forest-based modelling that underpins the 'omic offset calculation (Figure 4d). Although absolute values of offset are not directly comparable, range-wide patterns of offset can be compared among these methodologies. Alternatively, a single response matrix including allele frequencies, normalised read counts and methylation levels can be used to estimate a single value of 'omic (genomic-epigenomic) offset, although one may want to consider weighting multiple response variables depending on the context of the work. Integrating these datasets seems logical given their obvious interactions, with SNPs and structural variants associated with gene expression and epigenetic marks and with epigenetic variants contributing to structural variant formation (Bell et al. 2011; Li et al. 2012; Shi et al. 2020). Additionally, and in the context of climate change, Skinner et al. (2015) demonstrated how environment can induce epigenetic mutation and inheritance that results in genetic instability and ultimately promotes genetic mutation (i.e. CNVs) in later generations.

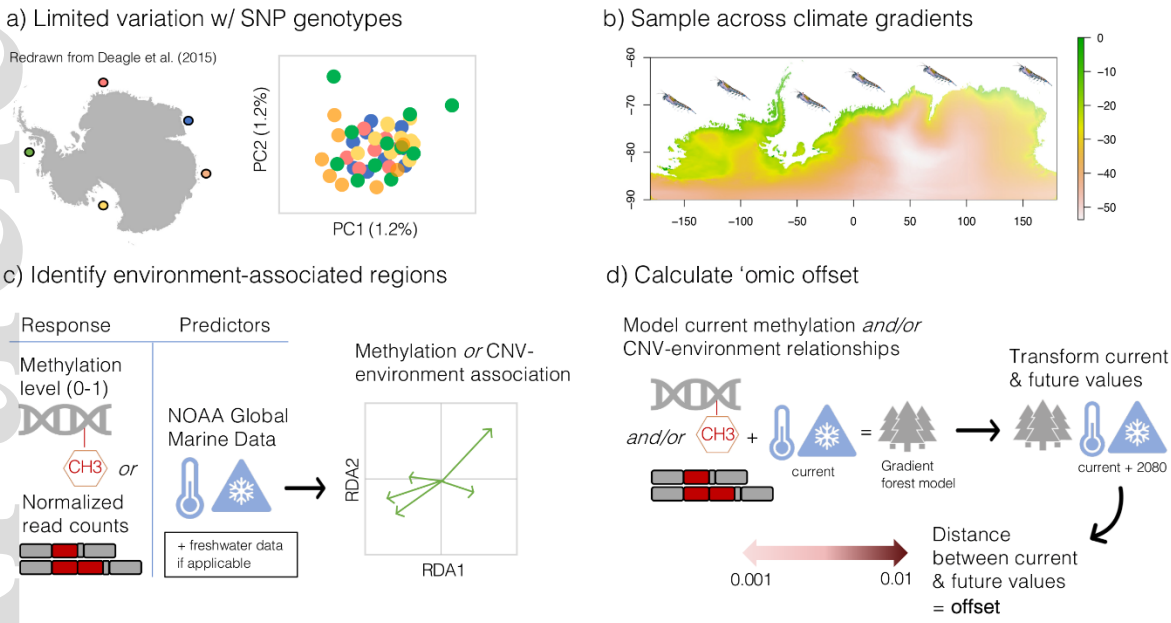

Figure 4: Multi-omics forecasting workflow. a) Principal components analysis (PCA) of Antarctic krill (*Euphausia superba*) SNP genotypes demonstrating panmixia (redrawn from Deagle et al. (2015)). b) Sampling across east-west environmental gradients in *E. superba*. Map displays annual mean temperature (°C; BIO1) from WorldClim (Fick & Hijmans 2017). Krill image derives from Wikimedia Commons and license details are available in Supplementary File 3. c) Response and predictor variables for RDA, to identify environment-associated regions. d) Pipeline for calculating 'omic offset (originally described by Fitzpatrick & Keller 2015).

4. *Conclusions & next steps*

It is becoming well established that the process of adaptation involves multiple forms of genetic and genomic variation. Here we suggest this diversity can be leveraged to better resolve fine-scale patterns in adaptation, improving power for future predictions of change, and at the same time supporting a more mechanistic understanding of biodiversity impacts and response due to climate change. This work promotes a shift from 'pattern' to 'process', providing insight into the mechanisms and processes behind a species' ability to rapidly adapt to environmental change. This builds on previous studies that have already established links between epigenetic processes and phenotypic plasticity of climate-related traits (Wong et al. 2019), and between copy number variation and accelerated adaptation to environmental change (Hull et al. 2018).

However, these methods are not without their challenges. First, because not all epigenetic variation is heritable, it is likely that some DMRs detected in the analysis may in fact represent plastic responses rather than true evolutionary change and future work will need to discern how best to disentangle these signals. Second, there still exists a risk of detecting false positives, as is the case with any association analyses (Finno et al. 2014), although this risk is lower with RDA than other methods (Forester et al. 2018). Additionally, any prediction of future climate change response would be strengthened by experimental work that seeks to validate these responses. For instance, Bogan et al. (2020) uncovered variable patterns of methylation in an Antarctic mollusc (*Limacina helicina antarctica*) when exposed to different acidity regimes that mimicked current and future ocean acidification, indicating a regulatory role of DNA methylation. This sort of work could be replicated across populations within a species to identify those with greater adaptive capacity, providing additional support for predictions of future climate change response. In all, incorporating other types of genomic and epigenomic variation into predictions will not only improve their power and robustness, but it also has the capacity to generate a paradigm shift in our understanding into the nature of intraspecific biodiversity and its response to change.

Data Availability

Data used in Figure 1 is available in Supplementary Files 1 and 2. Data used in Figure 2 is available at the Dryad repository from Layton et al. (2021) (https://doi.org/10.5061/dryad.8sf7m0ckd.). Data used in Figure 3 is available in Table S1 from Anastasiadi et al. (2021).

Author Contributions

Both authors conceived the ideas. K.K.S.L created the figures and led the writing of the manuscript. Both authors contributed critically to the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

References

Al-Breiki, R. D., Kjeldsen, S. R., Afzal, H. et al. 2018. Genome-wide SNP analyses reveal high gene flow and signatures of local adaptation among the scalloped spiny lobster (*Panulirus homarus*) along the Omani coastline. *BMC Genom*. 19, 690.

Anastasiadi, D., Venney, C. J., Bernatchez, L. et al. 2021. Epigenetic inheritance and reproductive mode in plants and animals. *Trends Ecol. Evol.*

Angers, B., Perez, M., Menicucci, T. et al. 2020. Sources of epigenetic variation and their applications in natural populations. *Evol. Appl.* 13, 1262– 1278.

Assis, J., Tyberghein, L., Bosch, S. et al. 2018. Bio-ORACLE v2.0: Extending marine data layers for bioclimatic modelling. *Global Ecol. Biogeogr*. 27, 277– 284.

Bay, R. A., Harrigan, R. J., Le Underwood, V. et al. 2018. Genomic signals of selection predict climate-driven population declines in a migratory bird. *Science* 359, 83–86.

Bell, J. T., Pai, A. A., Pickrell, J. K. et al. 2011. DNA methylation patterns associate with genetic and gene expression variation in HapMap cell lines. Genome Biol. 12, R10.

Bogan, S .N., Johnson, K. M. & Hofmann, G. E. 2020. Changes in genome-wide methylation and gene expression in response to future pCO2 extremes in the Antarctic pteropod *Limacina helicina antarctica. Front. Mar. Sci.* 6, 788.

Can, S. N., Nunn, A., Galanti, D. et al. 2021. The EpiDiverse Plant Epigenome-Wide Association Studies (EWAS) Pipeline. *Epigenomes* 5, 12.

Capblancq, T., Fitzpatrick, M. C., Bay R. A. et al. 2020. Genomic prediction of (mal)adaptation across current and future climatic landscapes. *Annu. Rev. Ecol. Evol. Syst.* 51, 245–269.

Chaisson, M. J. P., Sanders, A. D., Zhao, X. et al. 2019. Multi-platform discovery of haplotype-resolved structural variation in human genomes. *Nat. Commun.* 10, 1784.

Colella, J. P., Talbot, S. L., Brochmann, C. et al. 2020. Conservation genomics in a changing Arctic. *Trends Ecol. Evol.* 35, 149–162.

Conrad, D. F. & Hurles, M. E. 2007. The population genetics of structural variation. *Nat Genet.* 39(Suppl), S30–S36.

Deagle, B. E., Faux, C., Kawaguchi, S. et al. 2015. Antarctic krill population genomics: apparent panmixia, but genome complexity and large population size muddy the water. *Mol. Ecol.* 24, 4943–4959.

Donelson, J. M., Wong, M., Booth, D. J. et al. 2016. Transgenerational plasticity of reproduction depends on rate of warming across generations. *Evol. Appl.* 9, 1072–1081.

Dorant, Y., Cayuela, H., Wellband, K., et al. 2020. Copy number variants outperform SNPs to reveal genotype–temperature association in a marine species. *Mol. Ecol.* 29: 4765– 4782.

Fick, S. E. & Hijmans, R. J. 2017. WorldClim 2: new 1-km spatial resolution climate surfaces for global land areas. *Int. J. Climatol.* 37, 4302–4315.

Finno C. J., Aleman, M., Higgins, R. J. et al. 2014. Risk of false positive genetic associations in complex traits with underlying population structure: a case study. *Vet. J.* 202, 543–549.

Fitzpatrick, M. C. & Keller, S. R. 2015. Ecological genomics meets community-level modelling of biodiversity: mapping the genomic landscape of current and future environmental adaptation. *Ecol. Lett.* 18, 1–16.

Fitzpatrick, M. C., Chhatre, V. E., Soolanayakanahally, R. Y. et al. 2021. Experimental support for genomic prediction of climate maladaptation using the machine learning approach Gradient Forests. *Mol. Ecol. Resour.* 00, 1–17.

Flores, H., Atkinson, A., Kawaguchi, S. et al. 2012. Impact of climate change on Antarctic krill. *Mar. Ecol. Prog. Ser.* 458, 1–19.

Forester, B. R., Lasky, J. R., Wagner, H. H. et al. 2018. Comparing methods for detecting multilocus adaptation with multivariate genotype–environment associations. *Mol. Ecol.* 27, 2215–2233.

Fu, W., Zhang, F., Wang, Y. et al. 2010. Identification of copy number variation hotspots in human populations. *Am. J. Hum. Genet.* 87, 494–504.

Guerrero, R. F., Rousset, F. & Kirkpatrick, M. 2012. Coalescent patterns for chromosomal inversions in divergent populations. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 367, 430–438.

Gugger, P. F., Fitz-Gibbon, S., PellEgrini, M. et al. 2016. Species-wide patterns of DNA methylation variation in *Quercus lobata* and their association with climate gradients. *Mol. Ecol.* 25, 1665–1680.

Gunasekara, C. J., Scott, C. A., Laritsky, E. et al. 2019. A genomic atlas of systemic interindividual epigenetic variation in humans. *Genome Biol.* 20, 105.

Heckwolf M. J., Meyer, B .S., Häsler, R. et al. 2020. Two different epigenetic information channels in wild three-spined sticklebacks are involved in salinity adaptation. *Sci. Advances* 6, eaaz1138.

Herman, J. J. & Sultan, S. E. 2016. DNA methylation mediates genetic variation for adaptive transgenerational plasticity. *Proc. Biol. Sci.* 283, 20160988.

Hirase, S., Ozaki, H. & Iwasaki, W. 2014. Parallel selection on gene copy number variations through evolution of three-spined stickleback genomes. *BMC Genomics* 15, 735.

Hofmann, G. E. 2017. Ecological epigenetics in marine metazoans. *Front. Mar. Sci.* 4, 4.

Hull, R. M., Cruz, C., Jack, C. V. et al. 2017. Environmental change drives accelerated adaptation through stimulated copy number variation. *PLoS Biol*. 15, e2001333.

Imgenberg-Kreuz, J., Sandling, J. K., Almlöf, J. C. et al. 2016. Genome-wide DNA methylation analysis in multiple tissues in primary Sjögren's syndrome reveals regulatory effects at interferon-induced genes. *Ann. Rheum. Dis.* 75, 2029–2036.

Jarvie, S. & Svenning, J-C. 2018. Using species distribution modelling to determine opportunities for trophic rewilding under future scenarios of climate change. *Phil. Trans. R. Soc.* B37320170446.

Jiang, L., Zhang, J., Wang, J-J et al. 2013. Sperm, but not oocyte, DNA methylome is inherited by zebrafish early embryos. *Cell* 153, 773–784.

Kess, T., Bentzen, P., Lehnert, S. J. et al. 2020. Modular chromosome rearrangements reveal parallel and nonparallel adaptation in a marine fish. *Ecol. Evol.* 10: 638–653.

Kilada, R., Reiss, C. S., Kawaguchi, S. et al. 2017. Validation of band counts in eyestalks for the determination of age of Antarctic krill, *Euphausia superba*. *PLoS ONE* 12, e0171773.

Kooke, R. et al. 2015. Epigenetic basis of morphological variation and phenotypic plasticity in Arabidopsis thaliana. *Plant Cell* 27, 337–348.

Kronholm, I. & Collins, S. 2016. Epigenetic mutations can both help and hinder adaptive evolution. *Mol. Ecol.* 25, 1856–1868.

Kronholm, I., Bassett, A., Baulcombe, D. et al. 2017. Epigenetic and genetic contributions to adaptation in *Chlamydomonas*. *Mol. Biol. Evol.* 34, 2285–2306.

Küpers, L. K., Monnereau, C., Sharp, G. C. et al. 2019. Meta-analysis of epigenome-wide association studies in neonates reveals widespread differential DNA methylation associated with birthweight. *Nat. Commun.* 10, 1893.

Kurdyukov, S. & Bullock, M. 2016. DNA methylation analysis: Choosing the right method. *Biology* 5, 3.

Laurent, S., Pfeifer, S. P., Settles, M. L. et al. 2016. The population genomics of rapid adaptation: disentangling signatures of selection and demography in white sands lizards. *Mol. Ecol.* 25, 306–323.

Layton, K. K. S., Snelgrove, P. V. R., Dempson, J. B. et al. 2021. Genomic evidence of past and future climate-linked loss in a migratory Arctic fish. *Nat. Clim. Chang.* 11, 158–165.

Layton, K. K. S. Snelgrove, P. V. R., Dempson, J. B. et al. 2021. Genomic evidence of past and future climate-linked loss in a migratory Arctic fish, Dryad Dataset, https://doi.org/10.5061/dryad.8sf7m0ckd

Li, J., Harris, R. A., Cheung, S. W. et al. 2012. Genomic hypomethylation in the human germline associates with selective structural mutability in the human genome. *PLoS Genet.* 8, e1002692.

Liebl, A. L., Schrey, A. W., Richards, C. L. et al. 2013. Patterns of DNA methylation throughout a range expansion of an introduced songbird. *Integr. Comp. Biol.* 53, 351–358.

Lighten, J., Incarnato, D., Ward, J. et al. 2016. Adaptive phenotypic response to climate enabled by epigenetics in a K-strategy species, the fish *Leucoraja ocellata* (Rajidae). *R. Soc. Open Sci.* 3160299.

Liu, Q. A. 2013. The impact of climate change on plant epigenomes. *Trends Genet.* 29, 503–505.

Liu, Y., Weyrich, L. S. & Llamas, B. 2020. More Arrows in the Ancient DNA Quiver: Use of Paleoepigenomes and Paleomicrobiomes to Investigate Animal Adaptation to Environment. *Mol. Biol. Evol.* 37, 307–319.

McGuigan, K., Hoffmann, A. A. & Sgrò C. M. 2021. How is epigenetics predicted to contribute to climate change adaptation? What evidence do we need? *Phil. Trans. R. Soc. B* 376, 20200119.

Mérot, C., Oomen, R. A., Tigano, A. et al. 2020. A roadmap for understanding the evolutionary significance of structural genomic variation. *Trends Ecol. Evol.* 35, 561–572.

Münzbergová, Z., Latzel, V., Šurinová, M., et al. 2019. DNA methylation as a possible mechanism affecting ability of natural populations to adapt to changing climate. *Oikos* 128, 124–134.

Parker, L. M., O'Connor, W. A., Raftos, D. A. et al. 2015. Persistence of positive carryover effects in the oyster, *Saccostrea glomerata*, following transgenerational exposure to ocean acidification. *PLoS ONE* 10, e0132276.

Putnam, H. M., Davidson, J. M. & Gates, R. D. 2016. Ocean acidification influences host DNA methylation and phenotypic plasticity in environmentally susceptible corals. *Evol. Appl.* 9, 1165–1178.

Quan, C., Li, Y., Liu, X. et al. 2021. Characterization of structural variation in Tibetans reveals new evidence of high-altitude adaptation and introgression. *Genome Biol.* 22, 159.

Razgour, O. et al. 2019. Considering adaptive genetic variation in climate change vulnerability assessment reduces species range loss projections. *Proc. Natl Acad. Sci. USA* 116, 10418–10423.

Reinar, W. B., Lalun, V. O., Reitan, T. et al. 2021. Length variation in short tandem repeats affects gene expression in natural populations of *Arabidopsis thaliana*. *Plant Cell* 33, 2221–2234.

Ruiz-Arenas, C. & González, J.R. 2017. Redundancy analysis allows improved detection of methylation changes in large genomic regions. *BMC Bioinform*. 18, 553.

Schmid, M.W., Heichinger, C., Coman Schmid, D. et al. 2018. Contribution of epigenetic variation to adaptation in *Arabidopsis*. *Nat. Commun*. 9, 4446.

Shi, X., Radhakrishnan, S., Wen, J. et al. 2020. Association of CNVs with methylation variation. *Genom. Med.* 5, 41.

Siegert, M., Atkinson, A., Banwell, A. et al. 2019. The Antarctic Peninsula under a 1.5°C global warming scenario. *Front. Environ. Sci.* 7, 102.

Sinclair-Waters, M., Bradbury, I. R., Morris, C. J. et al. 2018. Ancient chromosomal rearrangement associated with local adaptation of a postglacially colonized population of Atlantic Cod in the northwest Atlantic. *Mol. Ecol.* 27: 339– 351.

Sjödin, P. & Jakobsson M. 2012. Population genetic nature of copy number variation. In: Feuk, L. ed. Methods in Molecular Biology. Springer New York, pp. 209–223.

Skinner, M. K., Guerrero-Bosagna, C. & Haque, M. M. 2015. Environmentally induced epigenetic transgenerational inheritance of sperm epimutations promote genetic mutations. *Epigenetics* 10, 762–771.

Skvortsova, K., Iovino, N. & Bogdanović, O. 2018. Functions and mechanisms of epigenetic inheritance in animals. *Nat. Rev. Mol. Cell Biol.* 19, 774–790.

Smith, G. & Ritchie, M. G. 2013. How might epigenetics contribute to ecological speciation? *Curr. Zool.* 59, 686–696.

Stanley, R. R. E., DiBacco, C., Lowen, B. et al. 2018. A climate-associated multispecies cryptic cline in the northwest Atlantic. *Sci. Advances* 4, eaaq0929.

Thapar, A. & Cooper, M. 2013. Copy Number Variation: What is it and what has it told us about child psychiatric disorders? *J. Am. Acad. Child Adolesc. Psychiatry* 52, 772-774.

Thorson, J. L., Smithson, M., Beck, D. et al. 2017. Epigenetics and adaptive phenotypic variation between habitats in an asexual snail. *Sci. Rep.* 7, 14139.

Tigano, A. & Friesen, V. L. 2016. Genomics of local adaptation with gene flow. *Mol. Ecol.* 25, 2144-2164.

Verhoeven, K. J. F., vonHoldt, B. M., Sork, V. L. 2016. Epigenetics in ecology and evolution: what we know and what we need to know. *Mol. Ecol.* 25, 1631–1638.

Veytia, D., Corney, S., Meiners, K. M. et al. 2020. Circumpolar projections of Antarctic krill growth potential. *Nat. Clim. Chang.* 10, 568–575.

Weeks, A. R., Smith, M. J., van Rooyen, A. et al. 2014. A single panmictic population of endemic red crabs, *Gecarcoidea natalis*, on Christmas Island with high levels of genetic diversity. Conserv. Genet. 15, 909–919.

Wellband, K., Mérot, C., Linnansaari, T., et al. 2019. Chromosomal fusion and life history-associated genomic variation contribute to within-river local adaptation of Atlantic salmon. *Mol. Ecol.* 28, 1439– 1459.

Wong, J. M., Kozal, L. C., Leach, T. S. et al. 2019. Transgenerational effects in an ecological context: conditioning of adult sea urchins to upwelling conditions alters maternal provisioning and progeny phenotype. *J. Exp. Mar. Biol. Ecol.* 517, 65–77.

Xu, L., Hou, Y., Bickhart, D. et al. 2016. Population-genetic properties of differentiated copy number variations in cattle. *Sci. Rep.* 6, 23161.

Yuan, J., Zhang, X., Wang, M. et al. 2021. Simple sequence repeats drive genome plasticity and promote adaptive evolution in penaeid shrimp. *Commun. Biol*. 4, 186.

Zimmerman, S. J., Aldridge, C. L. & Oyler-McCance, S. J. 2020. An empirical comparison of population genetic analyses using microsatellite and SNP data for a species of conservation concern. *BMC Genomics* 21, 382.