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OPINION

Ecology, the pace-of-life, epistatic selection and the maintenance of genetic variation in life-history genes

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Evolutionary genetics has long struggled with understanding how functional genes under selection remain polymorphic in natural populations. Taking as a starting point that natural selection is ultimately a manifestation of ecological processes, we spotlight an underemphasized and potentially ubiquitous ecological effect that may have fundamental effects on the maintenance of genetic variation. Negative frequency dependency is a well-established emergent property of density dependence in ecology, because the relative profitability of different modes of exploiting or utilizing limiting resources tends to be inversely proportional to their frequency in a population. We suggest that this may often generate negative frequency-dependent selection (NFDS) on major effect loci that affect rate-dependent physiological processes, such as metabolic rate, that are phenotypically manifested as polymorphism in pace-of-life syndromes. When such a locus under NFDS shows stable intermediate frequency polymorphism, this should generate epistatic selection potentially involving large numbers of loci with more minor effects on life-history (LH) traits. When alternative alleles at such loci show sign epistasis with a major effect locus, this associative NFDS will promote the maintenance of polygenic variation in LH genes. We provide examples of the kind of major effect loci that could be involved and suggest empirical avenues that may better inform us on the importance and reach of this process.

KEYWORDS
genome scans, haplotypes, inversion polymorphism, linkage, mitochondria, mtDNA, supergenes

Positive and negative natural selection generally erodes genetic variation and genetic drift further contributes to this decline. Despite the potential influx of new alleles through gene flow and mutation, we expect populations to have little genetic variation in those genes under selection. Yet, traits related to fitness, including life-history (LH) traits often have genetic variances exceeding those expected under mutation-selection balance (Barton & Keightley, 2002; Charlesworth, 2015; Charlesworth & Hughes, 2000). A major source of this excess variation is often considered to be balancing selection resulting from heterozygote advantage, antagonistic pleiotropy, negative frequency-dependent selection (NFDS) or from spatially or temporally varying directional selection. We currently lack strong evidence for their relative contributions, but recent evidence suggest that balancing selection indeed acts to maintain variation in LH traits (e.g. Barson et al., 2015; Charlesworth, 2015; Grieshop & Arnqvist, 2018; Hughes & Leips, 2006; Johnston et al., 2013; Remolina et al., 2012; Sharp & Agrawal, 2018).

A recent focus in LH research is the pronounced individual phenotypic variation within populations in suites of correlated rate-dependent LH traits, often referred to as pace-of-life (POL) syndromes (Réale et al., 2010; Ricklefs & Wikelski, 2002). In some cases, the distribution of such traits is even bimodal (e.g. Damsgård et al., 2019; Struelens et al., 2018), where some individuals show a relatively fast POL, characterized by high metabolic rate, small body size, short life span and early reproductive maturity, while others show a slower POL. This covariance among multiple LH traits is believed to arise from correlational selection (Réale et al., 2010) and a shared dependency on underlying physiological traits (Ricklefs & Wikelski, 2002), where metabolic rate constitutes a nexus (Brown et al., 2004, 2022; Burger et al., 2019). Suites of correlated behavioural traits are also sometimes incorporated into this framework (Réale et al., 2010). Ecological factors clearly have a central role in POL evolution (Dammhahn et al., 2018) and environmental conditions and suites of LH traits often covary across species in many groups (Stearns, 1983): species experiencing more frequent or severe resource limitation tend to show a slower POL compared to species living in environments where resource competition is less intense (Arnqvist et al., 2022).

Here, we bring attention to the fact that eco-evolutionary theory predicts the evolution and maintenance of polymorphism in POL phenotypes (Diekmann, 2003) and we argue that this may have important and underappreciated effects on the maintenance of variation in LH-related genes. Briefly, when resource availability is limited and organisms face trade-offs between competing demands, LH strategies that are relatively rare may enjoy a fitness advantage over the more common, leading to NFDS (Heino et al., 1998). In fact, negative frequency dependency is an emergent property of ecological density dependency and we expect this to be common (Heino et al., 1998; Kisdi, 1999) and to generate divergent POL phenotypes (Wolf et al., 2007). This well-known form of eco-evolutionary feedback has actually been recognized for decades. For example, Lewontin (1974) noted that 'if resources are in short supply and if each genotype exploits the resources in a slightly different way' then 'a genotype is its own worst enemy' and NFDS will be the result. Lewontin, in fact, insisted that frequency- and density-dependent selection is a major complication in our understanding of evolution (Lewontin, 2003). Thus, we use NFDS in its broadest possible sense (Heino et al., 1998) to also include scenarios where NFDS is an emergent property of ecological density dependence (Anderson, 1971; Antonovics & Kareiva, 1988; Bell et al., 2021; Clarke, 1979; Gallet et al., 2018; Kisdi & Geritz, 1999; Levene, 1953; Mallet, 2012; Wallace, 1975). This inclusive definition expands upon a narrower population genetic definition, where the fitness of a genotype is density independent and defined only by its frequency, to include more realistic and complex scenarios where NFDS emerges from density-dependent selection (Antonovics & Kareiva, 1988; Clarke, 1979; Kisdi, 1999; Mallet, 2012; Wallace, 1975). We note that theory predicts that this form of NFDS can favour the evolution of a genetic architecture which is 'concentrated' to one or a few regions, corresponding to polymorphisms in traits that are related to ecological competition (Kopp & Hermisson, 2006; Schneider, 2007; van Doorn & Dieckman, 2005; Yeaman, 2022).

Under various forms antagonistic or alternating selection, where optimal phenotypes differ in space or time, local density-dependent soft selection can effectively result in global NFDS (e.g. Gallet et al., 2018). We thus include in our discussion cases where stable polymorphism is traditionally not seen as being maintained by NFDS, but, for example, by spatially varying selection, where density dependence and NFDS may well be contributing to their maintenance. For example, clines in inversion frequencies with impacts on LH traits are well known. These clines are often interpreted as resulting from spatially varying selection, but experimental evidence from some of these suggest a role for NFDS (see below). This said, we note that the broader effects discussed below are predicted to emerge for protected polymorphism of any major effect locus affecting POL syndromes (POL loci), independent of precisely how selection operates to maintain that polymorphism.

The ubiquity of competition for limiting resources in natural populations (Gurevitch et al., 1992) suggests that disruptive and NFDS

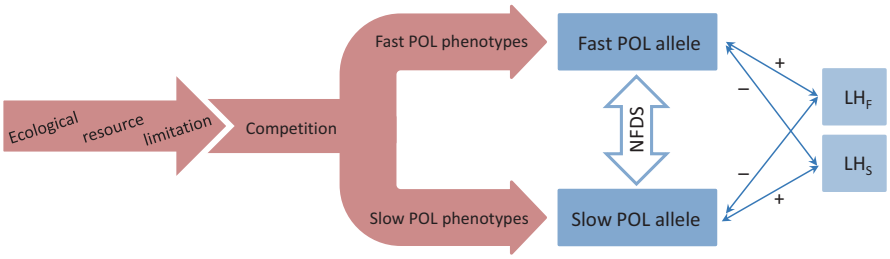

FIGURE 1 Competition for limiting ecological resources is often expected to result in disruptive selection within populations on traits that relate to resource use. This is predicted to lead to divergence and polymorphism in life-history (LH) phenotypes, reflecting alternative ways of utilizing resources. In some cases, a causal polymorphism in major effect loci affecting the 'pace-of-life' (POL) will thus be maintained by negative frequency-dependent selection (NFDS), as each allele or haplotype will essentially be its own worst competitor in resource competition. The maintenance of this polymorphism by NFDS will, in turn, have cascading effects on selection on a range of LH genes that show epistasis for fitness with this POL locus. For example, the F allele at a particular LH locus increases fitness when co-expressed with the Fast POL allele but decrease fitness when co-expressed with the Slow POL allele. If POL loci and LH loci affect distinct aspects of POL phenotypes, this would be manifested as correlational selection at a phenotypic level. We suggest that this process may generally act to elevate standing genetic variation in potentially many LH genes and we refer to this as associative NFDS.

on LH traits may frequently contribute to the maintenance of stable polymorphism in POL loci. Because LH traits are typically polygenic, any additional LH locus with more minor effects that adds to POL phenotypes will show diminishing rewards epistasis for fitness with POL loci (Whitlock et al., 1995). However, these epistatic effects should differ in sign across POL locus alleles (Figure 1). Briefly, we predict cascading effects of NFDS on selection at any LH locus that shows epistasis with POL loci. We refer to this scenario as associative NFDS (Figure 1). Here, we first ask whether there are any known examples of genes that may represent polymorphic POL loci segregating under NFDS in natural populations and warrant further study. We then ask what effects these polymorphisms should have on the maintenance of genetic variation in LH genes that interact with POL loci and, finally, we consider empirical efforts that would help shed light on the importance of these processes.

1 | MAJOR EFFECT LOCI AFFECTING POL AND NFDS

POL loci could represent sets of tightly linked genes or a single locus with major effects. Among the former, paracentric chromosomal inversions are prime candidates. These represent chromosomal stretches of varying length, often harbouring tens to hundreds or even thousands of functional genes, which are inverted in order. Because recombination rate is suppressed within inversion heterokaryotypes, enclosed genes segregate as one unit essentially making them 'supergenes' (Schwander et al., 2014).

The study of the evolutionary implications of inversions has a long and rich history (Hoffmann & Rieseberg, 2008; Kapun & Flatt, 2019; Wellenreuther & Bernatchez, 2018). Here, we highlight two specific insights from this body of research. First, variation in inversion genotype is associated with key LH and related phenotypes in many taxa, including metabolic syndromes, growth rate, body size, stress resistance, life span, development time, fecundity and viability (González, Ruiz-Arenas, et al., 2020; Hoffmann & Rieseberg, 2008; Pampoulie et al., 2023; Rane et al., 2015). Inversion polymorphism has also been directly associated with the regulation of genes that determine metabolism and energy production (Cheng et al., 2018; De Jong & Bochdanovits, 2003; Ibrahim et al., 2021). All of this suggests that inversions often affect multiple rate-dependent LH traits and enclose key LH genes. Second, there are many well-documented examples of geographical clines in inversion polymorphism where frequencies are associated with environmental gradients, some of which are even replicated on different continents (e.g. Kapun & Flatt, 2019; Wellenreuther & Bernatchez, 2018). Such clines are often ascribed to divergent directional selection in different parts of the cline, but are also consistent with balancing selection with environmental effects on equilibrium frequencies (Berdan et al., 2022). Here, density dependency and frequency dependency may be involved. The results of a number of laboratory cage culture experiments in several species of *Drosophila* are at least consistent with NFDS, as inversions return to intermediate frequencies after perturbation (Alvarez-Castro & Alvarez, 2005; Dobzhansky, 1992; Durmaz et al., 2020; Krimbas & Powell, 1992; Nassar et al., 1973; Tobari & Kojima, 1967). We note that the fact that recent efforts to understand the maintenance of inversion polymorphism has highlighted balancing selection (Berdan et al., 2022) is interesting in this regard, as inversions could represent unusually detectable and large effect variants that are symptomatic of underlying generally applicable evolutionary processes and amenable to study. Although much recent theory on inversions focuses on the accumulation of deleterious mutations and associative overdominance (e.g. Berdan et al., 2021), the above considerations suggest that inversions sometimes represent POL loci where polymorphism is instead maintained at least in part by NFDS. One striking example is the rainbow trout, where a major POL polymorphism appears to be maintained by NFDS (Christie et al., 2018) and is at least in part underlain by an inversion polymorphism (Pearse et al., 2019). Another is the seaweed fly *Coelopa frigida*, where inversion karyotypes differ in important LH traits (Mérot et al., 2020) and NFDS appears to play a role in the maintenance of geographical clines in inversion polymorphism (Mérot et al., 2018).

Many other types of structural variants besides inversions may also represent POL loci, such as variable number tandem repeat (VNTR) polymorphism including mini/microsatellites. One example may be the MAOA locus in primates. MAOA is an X-linked locus involved in the metabolism of neuropeptides that regulate behaviour in a wide sense. The promoter region of MAOA contains a VNTR polymorphism in humans, where the 3R and 4R variants of a 30 bp tandem repeat motif are the two common alleles present, which differentially affect transcription of MAOA. Three facts suggest that this VNTR may represent a POL locus. First, allelic VNTR variation has been associated with a large number of phenotypes in humans. Most of these are rate-dependent behaviours (Ficks & Waldman, 2014), including food intake and growth, but they also include LH phenotypes related to metabolic syndromes (Dias et al., 2016). Second, VNTR polymorphism in humans is ubiquitous and show similar allele frequencies across populations, in a variety of geographical locations. The frequency of the 3R allele ranges between 29% and 61% and that of the 4R allele between 36% and 71% (Caspi et al., 2002; Deckert et al., 1999; Sabol et al., 1998; Widom & Brzustowicz, 2006). Third, several other primates harbour analogous VNTR polymorphisms in the MAOA promoter region (Choi et al., 2014; Inoue-Murayama et al., 2006; Wendland et al., 2006), although the repeat sequence motif differs, suggesting an ancient trans-specific functional polymorphism in this region. These facets of MAOA variation are consistent with NFDS in this region, and NFDS generated by competitive interactions has been suggested to act to maintain VNTR variation (McDermott et al., 2009).

Colour polymorphism provides several classic examples of NFDS (Svensson, 2017). An intriguing possibility is that such phenotypic markers may be closely integrated with physiological processes that have important LH consequences (Svensson et al., 2020). Genetic regions dictating colour may then represent POL loci, or may interact with POL loci, and be subject to

associative NFDS. One potential example are the colour morphs of female *Colias* butterflies that also differ in POL, a phenotype recently mapped to a transposable element insertion (Woronik et al., 2019). Another may be the degree of melanization more generally (Ethier & Despland, 2012) as melanin production is intimately linked to life histories. Interestingly, a region responsible for polymorphic light/dark coloration is in strong linkage disequilibrium with an inversion known to be associated with POL in some populations of *D. melanogaster* (Takahashi & Takano-Shimizu, 2011; Telonis-Scott & Hoffmann, 2018), consistent with strong epistatic selection. Similarly, colour polymorphism in owls maps to genes in the melanin pathway (Cumer et al., 2023) is associated with both metabolic rate (Mosher & Henny, 1976) and key LH traits (Da Silva et al., 2013; Kvalnes et al., 2022) and is likely maintained by processes similar to those discussed here (Roulin, 2004).

Structural POL loci may also involve copy number variants of coding genes. A recent potential example is the polymorphism in copy number of TOR located on the Y-chromosome of seed beetles (Kaufmann et al., 2023). Two alternative Y haplotypes (single TOR copy and three TOR copies) segregate in at least one natural population and have very pronounced effects on male body size (Kaufmann et al., 2021) and growth rate (Kaufmann et al., 2023). Interestingly, TOR is a major LH gene showing signs of balancing selection in other systems (see below) and Y polymorphism in seed beetles may thus reflect balancing selection though NFDS, which apparently contributes to the maintenance of Y polymorphism in some other taxa (e.g. Sandkam et al., 2021; Van Hooft et al., 2018).

We suggest that another likely example of a POL locus is mitochondrial DNA. Mitochondrial DNA (mtDNA) can be thought of as a supergene (Ballard & Melvin, 2010) which typically carries 13 co-segregating genes along with sites that affect mitochondrial transcription and translation and is somewhat special as it is maternally inherited, haploid and does not recombine. Because mtDNA genes encode for parts of the very heart of metabolism—the ATP-producing OXPHOS pathway—there are very good reasons to regard mtDNA as candidate POL loci. We highlight two specific facets of recent research on mtDNA that support this view. First, within-population mtDNA polymorphism is very common, but was long assumed to be non-functional and neutral. However, recent research has associated mtDNA polymorphism with key rate-dependent LH and related phenotypes, such as development time (Christie et al., 2004; Erić et al., 2022), longevity (Jelić et al., 2015), stress resistance (Jelić et al., 2015; Sun et al., 2019), general activity (Ueno & Takahashi, 2021) and even metabolic rate (Baris et al., 2017; Đorđević et al., 2016; Kurbalija Novičić et al., 2015). Second, observations such as those of stable mtDNA haplotype frequencies over time and space (Andrianov et al., 2008; Oliver et al., 2005), environmental clines in haplotype frequencies (McKenzie et al., 2019; Silva et al., 2014) and widespread polymorphism of deeply divergent mtDNA haplotype families (Kvie et al., 2013) are all consistent with balancing selection. If we accept the tenet that mtDNA may represent a POL locus, this has an important implication: the fact that overdominance cannot occur in the haploid mtDNA points to NFDS in the maintenance of these polymorphisms. Several laboratory experimental evolution studies of insects have actually shown that mtDNA haplotype frequencies tend return to intermediate frequencies when perturbed (Kazancıoğlu & Arnqvist, 2014; Kurbalija Novičić et al., 2020; MacRae & Anderson, 1988; Oliver et al., 2005).

Single major effect loci may of course also represent POL loci. However, associating variation in complex LH traits even with loci with major effects is difficult (Schielzeth et al., 2018) and detecting NFDS at particular sites is even more difficult (Bitarello et al., 2023; Fijarczyk & Babik, 2015). Hence, it is perhaps not surprising that there are few well-studied examples. One possible example may be the *for* locus in *D. melanogaster*, which codes for a cGMP-dependent protein kinase. Allelic variation here is associated with rate-dependent LH traits (Kaun et al., 2007; Kent et al., 2009), experiences NFDS in at least some laboratory environments (Fitzpatrick et al., 2007) and there is some evidence that natural populations are polymorphic (Sokolowski et al., 1997). A second example may be the npr-1 locus in *Caenorhabditis elegans* (Gloria-Soria & Azevedo, 2008). Allelic variants in this region are associated with rate-dependent LH traits (Andersen et al., 2014) and experimental evidence is consistent with polymorphism being maintained in the laboratory by balancing selection (Gloria-Soria & Azevedo, 2008; Greene et al., 2016).

A third example may be genes in the AMPK (AMP-activated protein kinase) signalling complex, such as the SNF4Aγ locus in *Drosophila* flies. This gene shows intermediate frequency and shared clinal polymorphism in *D. melanogaster* and *D. simulans* (Fabian et al., 2015; Mallard et al., 2018), consistent with a role for long-term balancing selection. Furthermore, it bears the hallmarks of an LH locus as it is involved in sensing the availability of nutrients and energy and in the regulation of cell growth (González, Hall, et al., 2020; González, Ruiz-Arenas, et al., 2020) and is known to affect life span in *D. melanogaster* (Tóth et al., 2008).

A fourth example is genes in the insulin/insulin-like (IIS) / target-of-rapamycin (TOR) signalling pathway. This well-known pathway plays a major role in nutrient sensing and energy homeostasis, and has well-documented effects on key LH traits (such as growth, metabolism and ageing) in diverse taxa. In *Drosophila*, several genes in the IIS/TOR pathway show clinal polymorphism shared across continents (Fabian et al., 2015), consistent with balancing selection. In-depth studies of one of these have shown that the clinal alternative alleles indeed affect fat metabolism, viability and body size (Betancourt et al., 2021; Durmaz et al., 2019; Paaby et al., 2014). In humans, the gene RPTOR also shows clinal polymorphism shared across continents, which correlates with environmental factors (Hancock et al., 2008), suggesting balancing selection (Novembre & Di Rienzo, 2009). In addition to these examples, we note that there are many cases of apparently stable polymorphism in loci with major effects on metabolism and growth, such as the PGM locus in dung flies (Ward et al., 2004) and the LDH-B locus in killifish (DiMichele & Powers, 1982).

2 | POL LOCI AND THE MAINTENANCE OF GENETIC VARIATION IN RELATED LH GENES

We have outlined a scenario where resource competition results in NFDS for divergent life histories that, in turn, generates stable polymorphism in POL loci. However, LH traits are polygenic and LH phenotypes will thus be affected by many additional loci, many of which are physically unlinked with the POL locus. For example, there is evidence that mtDNA shows epistasis with nuclear loci for LH traits (Rand, 2017; Wolff et al., 2014). We predict that many LH-related loci will show epistatic interactions with POL loci in a manner where alternative variants are favoured by selection when residing with each alternate allele or haplotype of the POL locus. Balancing selection though NFDS in a POL locus would then have cascading effects on selection in many other LH loci. For example, an allele which increases development rate may elevate fitness when co-expressed with a fast POL locus allele but depress fitness with a slow POL locus allele. In theory, we thus expect segregating POL loci to generate widespread epistatic selection involving many LH loci through what we term associative NFDS (Figure 1).

If stable polymorphism in POL loci is maintained in a population by NFDS, then we predict that variation in epistatically interacting LH loci will be elevated as a result of a reduced rate of fixation. In essence, POL loci can be thought of as alternate environments in which segregating alleles at polymorphic loci find themselves expressed at a frequency that matches the POL locus variants' frequency in the population. It is easy to imagine that some alleles at LH loci are favoured when co-expressed with one POL allele but disfavoured with the other. This form of antagonistic selection bears similarities to that arising from temporal or spatial environmental variation or sex-specific selection (Hoekstra, 1975; Levene, 1953; Prout, 2000). Here, the alternate alleles or haplotypes of the POL loci constitute the environments, and the opposing selection results from epistatic interactions, rather than gene × environment or gene × sex interactions. In light of prior theory on balancing selection resulting from such antagonistic selection, we would expect the impact on the persistence of polymorphism in these unlinked loci to be greatest when alternating or opposing selection is strong and symmetrical or when there are dominance reversals for fitness leading to net heterozygote advantage (Charlesworth & Hughes, 2000; Connallon & Chenoweth, 2019; Hedrick, 1986; Hoekstra, 1975; Posavi et al., 2014; Prout, 2000; Wittmann et al., 2017). In addition, as is true for both gene × environment (Felsenstein, 1976) and gene × sex interactions (Kidwell et al., 1977), epistasis between POL and other LH loci will generate overdominance for fitness under reasonable conditions. This is because the harmonic mean fitness will tend to be highest for heterozygotes in both loci since fitness variance over different genetic backgrounds tends to be lowest for heterozygotes.

A useful analogy for POL loci and epistatically interacting LH alleles is sex and sexually antagonistic alleles. Here, the two sexes (the genetic environments) are maintained by NFDS at a ratio of 1:1 and segregating alleles in autosomal loci will find themselves in a male or a female environment about 50% of the time. The expectation is that alleles that are beneficial to both sexes, or beneficial in one and neutral in the other, will soon fix under net directional selection. However, if loci have alternate alleles that are beneficial in one sex but detrimental to the other, sexually antagonistic selection can lead to their maintenance. While the conditions required for a protected polymorphism by balancing selection are fairly narrow, they are widened considerably by dominance reversals between the sexes (Arnqvist et al., 2014; Fry, 2010; Kidwell et al., 1977) and recent data suggest that these may be more common than previously expected (Barson et al., 2015; Grieshop & Arnqvist, 2018; Meiklejohn et al., 2014; Pearse et al., 2019). In fact, the conditions for dominance reversals may be widespread (Connallon & Chenoweth, 2019; Otto & Bourguet, 1999; Wittmann et al., 2017). Even in the absence of dominance reversals, sexually antagonistic selection can elevate standing genetic variance by elevating the persistence time of alternate alleles (Connallon & Chenoweth, 2019; Connallon & Clark, 2012, 2014).

While NFDS in a POL locus no doubt will affect selection in other loci through epistasis (e.g. Udovic, 1980), the effects of this on the maintenance of variation in other loci will critically depend on the rate of recombination (Neher & Shraiman, 2009). Needless to say, the longevity of polymorphism at these loci would be much promoted if they were physically linked to the POL locus. There are reasons to believe that linkage may evolve. One means would be the evolution of LD via epistatic selection or through assortative mating by fitness or LH traits, mediated by for example segregation of LH phenotypes in space or time. The latter is likely to occur when POL variation affects reproductive timing, in which case assortative mating by time should result in LD and in recurrent seasonal clines in allele frequencies (Fox, 2003; Hendry & Day, 2005; Weis & Kossler, 2004). Observations of seasonal clines in allele frequencies are common and are sometimes known to involve candidate POL loci such as inversions (e.g. Machado et al., 2021; Rodriguez-Trelles et al., 1996; Rudman et al., 2022) and mtDNA (e.g. Christie et al., 2010). We also note that one would predict that epistatic selection for co-segregation between POL variants and favourable LH alleles at other loci would favour physical linkage, either though translocation of these loci or through stepwise extension of POL inversions to recruit additional LH loci, leading to sequential recombination suppression and the generation of evolutionary strata within inversions (Huang & Rieseberg, 2020) analogous to that seen in some sex chromosomes (Wright et al., 2016).

3 | WHAT DO WE NEED?

Detecting balancing selection in general, and NFDS in particular, is very challenging (Bitarello et al., 2023; Fijarczyk & Babik, 2015). The standard empirical toolbox we use to better understand selection and adaptation using genomic data, based largely on various forms of outlier detection, will typically not able to detect and shed much light on associative NFDS (Fijarczyk & Babik, 2015; Wellenreuther

& Hansson, 2016). The fact that key LH phenotypes are typically highly polygenic further exacerbates the challenge (Barton, 2022; Csilléry et al., 2018). As a consequence, inferences based solely on genome scans and reverse genetics of adaptation will necessarily assign a very biased view of the role of NFDS in maintaining variation (Bomblies & Peichel, 2022; Fijarczyk & Babik, 2015; Tiffin & Ross-Ibarra, 2014). Here, we suggest that there are several lines of enquiry that may prove helpful in determining the importance and reach of NFDS in maintaining variation in LH-related genes.

3.1 | Identifying candidate POL loci

The phenotypic manifestations of major effect loci have been investigated for inversions (Hoffmann & Rieseberg, 2008) and mtDNA (Wolff et al., 2014). We have noted that these are candidate POL loci, in part because they have significant effects on metabolic rate and life histories. Yet, few studies have asked whether these candidate POL loci actually map to known POL variation in that species. For example, the effects of POL loci on metabolic rate are not generally well investigated, although there are a few examples (Gangloff et al., 2020; Kurbalija Novičić et al., 2015; Pichaud et al., 2012). Moreover, a much broader and deeper understanding of the LH consequences of polymorphism in candidate POL loci would be useful. For example, POL loci should be significantly enriched with genes involved in metabolic processes, reflecting the central role of metabolic rate in life histories (Brown et al., 2004, 2022; Burger et al., 2019; Kapun et al., 2016). While this is per definition true for mtDNA, improved annotation and enrichment analyses of polymorphic inversions would be interesting in this regard (e.g. Rane et al., 2015).

3.2 | Identifying NFDS on candidate POL loci

Experimental studies where replicated populations are seeded with known allele frequencies of major effect loci and where allele frequency dynamics are then tracked over time can implicate NFDS (Alvarez-Castro & Alvarez, 2005; Dobzhansky, 1992; Durmaz et al., 2020; Kazancıoğlu & Arnqvist, 2014; Krimbas & Powell, 1992; Kurbalija Novičić et al., 2020; MacRae & Anderson, 1988; Nassar et al., 1973). This approach would be profitably extended to candidate POL loci. The straightforward prediction being that after perturbation, allele frequencies will return to intermediate values if NFDS is operating. If competition between alleles is implicated in their maintenance, it can be tested by experimentally varying the degree of resource competition across evolving populations (Kurbalija Novičić et al., 2020). Short-term experimental fitness assays of major effect loci as a function of their allele frequencies and the level of resource competition can provide evidence for NFDS and is useful in this regard (Fitzpatrick et al., 2007), and could also be extended to experimental evolution. Ideally, such studies would be performed in nature or under conditions that mimic natural conditions. In cases where allele frequency time-series data are available for POL loci, it is also possible to infer NFDS by fitting specific population-genetic models to data (e.g. Arnqvist et al., 2016; Le Rouzic et al., 2015; O'Hara, 2005).

3.3 | POL loci and epistasis

Under the tenet that POL loci should show epistasis with unlinked loci which act to maintain genetic variation in these loci (Figure 1), we predict a negative genetic correlation in fitness across segregating background genetic variation when co-expressed with alternative POL loci variants. The logic here is that those alleles that yield high fitness with one POL locus variant should tend to show low fitness with the other, borrowing from the rationale used to demonstrate standing sexually antagonistic genetic variation (e.g. Chippindale et al., 2001; Connallon & Matthews, 2019). We know of no directly relevant data, but this could in principle be tested by expressing different POL locus genotypes in different genetic backgrounds (e.g. isogenic lines), although relative fitness must be assayed in a competitive environment with all POL locus variants present. Alternatively, data from natural populations could be used to assess sign epistasis for fitness between POL loci and other variants based on pedigree-data (Brommer et al., 2007).

3.4 | Allele frequency spectra for LH genes

It is possible that analyses of population genomic data could add to our understanding of associative NFDS, but it is unclear how firm such inferences can be. For example, we would predict that many key LH genes should show a relatively even frequency spectrum of segregating sites. Yet, several confounding processes can generate such spectra (Bitarello et al., 2023; Fijarczyk & Babik, 2015) and, to further complicate matters, the polygenic nature of LH variation predicts substantial genetic redundancy. One strategy is to interrogate sets of genes showing hallmarks of balancing selection for functional enrichment. Efforts along these lines have revealed an enrichment of genes involved in the regulation of metabolic processes both in a few animals (Arnqvist & Sayadi, 2022; Croze et al., 2017) and plant pathogens (Castillo & Agathos, 2019). Another approach might be to ask whether genes likely affecting variation in POLS show allele frequency spectra different from those of other gene sets.

3.5 | Modelling the effect of POL loci on epistatically interacting loci

We have argued that the maintenance of POL loci by NFDS will elevate variation in epistatically interacting LH genes. This inference is to a large part based on models of the impact of sexually antagonistic selection on the maintenance of variation (Connallon & Clark, 2012; Prout, 2000). Here, we are assuming the two sexes

are equivalent to two alternate alleles of a POL locus. We think this is reasonable, as both are persistent polymorphisms and both are expected to show epistasis with many other loci. However, they differ in one potentially important way that warrants further modelling. While sex is in theory maintained by NFDS, chromosomal sex determination fixes sex ratio at 1:1. Our argument with POL loci is that NFDS is actively maintaining intermediate frequencies of the polymorphism. Relative to chromosomally determined sex, it is possible that stronger selection in the POL locus may elevate the effect on maintenance of variation in epistatically interacting loci, and reduce the potential for drift. Modelling efforts aimed at characterizing the conditions under which the processes discussed here will elevate genetic variation in LH genes would be very valuable. Such models would preferably need to explore the effects of varying recombination rate, assortative mating and dominance reversal on the effects of associative NFDS.

3.6 | Dominance reversal

Epistasis for fitness between a sex-determining locus and other loci is expected to result in sex-specific dominance reversal in the latter loci (Spencer & Priest, 2016) and this prediction has some empirical support (Barson et al., 2015; Grieshop & Arnqvist, 2018; Meiklejohn et al., 2014; Pearse et al., 2019). In fact, theory predicts that dominance reversals should evolve under a wide set of conditions (Connallon & Chenoweth, 2019; Otto & Bourguet, 1999) and we suggest that POL phenotypes could be one. Under this hypothesis, we predict that allelic dominance in LH loci would tend to be swapped between slow and fast POL genotypes.

3.7 | Evolutionary strata in inversions

If inversion polymorphism is maintained by NFDS involving POL phenotypes, we predict that inversions could swell through stepwise extension to recruit adjacent LH loci, leading to sequential recombination suppression and the generation of evolutionary strata within inversions. This prediction is based on a number of assumptions and may not always apply, but a few studies in plants have indeed identified such strata (Huang & Rieseberg, 2020).

3.8 | Seasonal clines in allele frequencies

As detailed above, to the extent that POL involves temporal traits such as timing of reproduction, we predict that selection and assortative mating should generate a pattern of LD that could be detected as seasonal clines in allele frequencies in LH genes. It is interesting to note that such clines seem quite common and characterizing the genes or genomic regions that make up these clines would likely help us understand the processes that generate them (Hendry & Day, 2005).

3.9 | POL in sister taxa

We have argued that NFDS on major loci, and associated epistatic effects can maintain variation, which, in turn, may fuel adaptation and population differentiation. There is increasing evidence for adaptation and speciation from standing genetic variation (Bomblies & Peichel, 2022; Schluter & Rieseberg, 2022). Whether processes we describe here results in polymorphism or contributes to branching and speciation will depend on a number of factors (Rueffler et al., 2006). To the extent that it results in speciation, we would predict that closely related sister taxa would often (i) show disproportionate divergence in key LH genes and (ii) show opposing POL phenotypes especially under sympatric or parapatric speciation.

4 | CONCLUSIONS

The potential impacts of NFDS on the maintenance of variation are well known. Yet, we feel, this potential is currently worth increased attention and extension for a few reasons. Frequency dependency is clearly a very central process in the maintenance of ecological diversity (Chesson, 2000), suggesting that it is likely a central process also in the maintenance of genetic diversity. Furthermore, because competition for limiting resources is clearly very widespread in nature (Gurevitch et al., 1992), the potential for density dependence to generate NFDS involving LH traits may be near ubiquitous (Lewontin, 1974) and the processes discussed here significant for this reason alone. We have suggested that our quest to better understand the processes that act to maintain genetic variation can profit from a closer conceptual integration of the processes that are known to act to maintain ecological diversity (Pelletier et al., 2009) and that such integration is promoted by a more inclusive definition of NFDS. In particular, we argue that NFDS on major effect genes should be an emergent property of disruptive selection on LH syndromes, manifested as variation in POL phenotypes. Such NFDS may then contribute to associative NFDS in many other loci that show epistasis with such major effect genes, resulting in the elevation of standing genetic variation in a large number of LH related genes. We note that while the tools that we typically use to better understand selection and adaptation using genomic data are well equipped to detect selective sweeps, they are ill-suited to assess the role of NFDS in maintaining LH variants. We suggest some lines of enquiry that we believe would help promote a closer and more fruitful integration of ecological processes and molecular genetics.

AUTHOR CONTRIBUTIONS

Conception: G.A. Development of concepts and ideas: G.A. and L.R. Drafting the article: G.A. and L.R.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

No data or scripts have been generated for this article.

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