OXFORD GENETICS

GENETICS, 2024, 228(3), iyae151
https://doi.org/10.1093/genetics/iyae151
Advance Access Publication Date: 18 October 2024
WormBook

Life history in *Caenorhabditis elegans*: from molecular genetics to evolutionary ecology

Christian Braendle [1,*] Annalise Paaby [2,*]

[1]Université Côte d'Azur, CNRS, Inserm, Institut de Biologie Valrose, 06108 Nice, France
[2]School of Biological Sciences, Georgia Institute of Technology, Atlanta, GA 30332, USA

*Corresponding authors: Christian Braendle, Université Côte d'Azur, CNRS, Inserm, Institut de Biologie Valrose, Parc Valrose, 06108 Nice, France. Email: christian.braendle@univ-cotedazur.fr; Annalise Paaby, School of Biological Sciences, Georgia Institute of Technology, Atlanta, GA 30332, USA. Email: paaby@gatech.edu

Life history is defined by traits that reflect key components of fitness, especially those relating to reproduction and survival. Research in life history seeks to unravel the relationships among these traits and understand how life history strategies evolve to maximize fitness. As such, life history research integrates the study of the genetic and developmental mechanisms underlying trait determination with the evolutionary and ecological context of Darwinian fitness. As a leading model organism for molecular and developmental genetics, *Caenorhabditis elegans* is unmatched in the characterization of life history-related processes, including developmental timing and plasticity, reproductive behaviors, sex determination, stress tolerance, and aging. Building on recent studies of natural populations and ecology, the combination of *C. elegans*' historical research strengths with new insights into trait variation now positions it as a uniquely valuable model for life history research. In this review, we summarize the contributions of *C. elegans* and related species to life history and its evolution. We begin by reviewing the key characteristics of *C. elegans* life history, with an emphasis on its distinctive reproductive strategies and notable life cycle plasticity. Next, we explore intraspecific variation in life history traits and its underlying genetic architecture. Finally, we provide an overview of how *C. elegans* has guided research on major life history transitions both within the genus *Caenorhabditis* and across the broader phylum Nematoda. While *C. elegans* is relatively new to life history research, significant progress has been made by leveraging its distinctive biological traits, establishing it as a highly cross-disciplinary system for life history studies.

Keywords: androdioecy; adaptation; complex trait; *Caenorhabditis*; *Caenorhabditis elegans*; Darwinian fitness; fitness components; life cycle; life history evolution; natural variation; nematodes; phenotypic plasticity; reproductive mode; reproductive plasticity; trade-offs; WormBook

Introduction

At its most essential, the success of an organism is defined by its genetic contribution to the next generation. Thus, the lifetime reproductive performance of an organism, known as Darwinian fitness, is the ultimate target of natural selection and its variation is the fundamental source for adaptative evolution (Fisher 1930; Lewontin 1974; Charlesworth 1994; Falconer and Mackay 1996; Walsh and Lynch 2018). But what determines lifetime reproductive success? "Life history" refers to the principal phenotypic traits over an organism's life cycle that govern its survival and reproduction in the face of challenges imposed by the environment; these typically include aspects of timing and resource investment such as developmental rate, maturation schedule, reproduction, and survival (Stearns 2000).

A hallmark of life history is that traits exhibit interdependencies that drive constraints and trade-offs (Box 1). For example, an individual may produce large offspring or many offspring, but not many large offspring. How natural selection optimizes such trade-offs has been a central objective of life history research since its inception (Fisher 1930; Lack 1954; Williams 1966; Roff 1992; Stearns 1992). While any trait may be considered a life history trait if it affects fitness, the most relevant are those that most directly influence an organism's reproduction and survival schedule. As such, research into the genetic or physiological mechanisms that govern life history phenotypes, like developmental rate or fecundity, is integral to life history research. Yet, their fitness values are strongly dependent on context, making them challenging to accurately capture and place within life history theory (Boxes 1 and 2).

One of the great challenges in current biology is to integrate how molecular, physiological, and quantitative genetic mechanisms can shape such life history traits and how their differential regulation contributes to life history variation within and between species. While its long history of molecular and developmental genetics research established *Caenorhabditis elegans* as a model organism, momentum for evolutionary investigations in *C. elegans* has emerged only in the past two decades (Teotónio *et al.* 2017),

Received on 09 July 2024; accepted on 11 September 2024

Box 1. Trade-offs, fitness, and life history theory

Trade-offs are central to life history. Without trade-offs between traits, selection should maximize fitness-associated phenotypes to the limits of physiology and history; the fact that organisms exhibit suboptimality and variation in individual fitness-related traits indicates that relationships between traits are embedded in the biology of the organism (Stearns 1989).

For example, the fundamental trade-off at the heart of life history is the relationship between reproduction and longevity: investment in reproductive success early in life comes at the cost, 1 way or another, of surviving to reproduce later (Fisher 1930; Williams 1966; Kirkwood 1977; Bell 1986). Whichever strategy maximizes genetic contribution to future generations is the optimal one, but the traits that define it will depend on context, such as resources in the current and future environment. For *C. elegans*, which can enter dauer to persist through suboptimal conditions, an essential question is whether to develop directly to reproductive maturity or to pause development as an investment in future opportunity. As we discuss elsewhere (Box 3), the propensity to enter dauer is not fixed; *C. elegans* genotypes exhibit variability in dauer induction from environmental cues, and only a subset of trait values will maximize fitness under a given selection regime. Ultimately, the generic form of the optimal life history strategy is the age-specific reproduction and mortality schedule that maximizes fitness.

Evolutionary biologists have always centered the concept of fitness in the study of life history strategy, but much of the literature that contributes to our understanding of life history traits does not address fitness directly. For example, aspects of developmental timing, fecundity, and stress tolerance all contribute to age-specific schedules of reproduction and survival, but the reach of our understanding into these biological phenomena, particularly in a model system like *C. elegans*, extends primarily to their genetic and physiological mechanisms. These findings are deeply informative with respect to the organismal adaptations that govern life history strategy, but they often stop short of testing key hypotheses in life history theory if they do not consider fitness.

How do we assess fitness? The most general representation is given by the intrinsic population growth rate (r), a single fitness metric that integrates lifetime offspring production, reproductive timing, and survival (Roff 1992; Carey 2001). In an experimental setting, r may be estimated from increases in population size in culture. It can also be derived from single-generation data following the construction of demographic life tables, wherein a cohort of individuals are monitored from birth to death to ascertain fecundity and survivorship schedules; both methods have been employed in nematode research (Hodgkin and Barnes 1991; Shook and Johnson 1999; Vassilieva and Lynch 1999; Vassilieva *et al.* 2000; Chen *et al.* 2006, 2007; Dolgin *et al.* 2007; Diaz *et al.* 2008; Muschiol *et al.* 2009; Anderson, Albergotti *et al.* 2011). Now, with the ease and affordability of DNA sequencing, relative fitness is more likely to be assessed from competing strains or genotypes in shared culture, by capturing frequency changes of relevant alleles (Walker *et al.* 2000; Jenkins *et al.* 2004; Ashe *et al.* 2013; Chelo and Teotónio 2013; Savory *et al.* 2014) or neutral barcodes (Zhao *et al.* 2018; Long *et al.* 2023).

Life history theory is the analytical framework that aims to elucidate organismal strategies for maximizing fitness, including the traits that comprise life history, their relationships, underlying mechanisms, and evolution (Roff 1992; Stearns 1992). Ultimately, this requires the integration of fitness estimates with organismal trait information, including mechanisms of phenotype determination from molecular and developmental genetics research and the nature of trait variation, covariation, and architecture from evolutionary and quantitative genetics.

largely driven by collections of wild strains by the community and construction of open resources for quantitative genetic and genomics analyses (Barrière and Félix 2005b; Félix and Braendle 2010; Frezal and Félix 2015; Cook *et al.* 2017; Lee *et al.* 2021; Andersen and Rockman 2022; Crombie *et al.* 2024). Thus, *C. elegans* offers a singular contribution to life history research, an especially interdisciplinary field, via the union of deep mechanistic understanding at the organism level with more recent characterizations of intra- and interspecific trait variation. Here, we summarize what several decades of research on *C. elegans* has taught us about its life history and how this nematode has advanced our understanding of major questions in the life history framework.

Historical context

C. elegans was discovered by Emile Maupas at the end of the 19th century and, as usual for taxonomic work, his characterization included a basic description of life history and reproductive mode, as well as a comparison of these features to other nematode taxa (Maupas 1899, 1900). *C. elegans* and other free-living nematodes initially sparked interest in varied research, particularly for studying reproductive systems and underlying genetics of sex determination (Nigon and Félix 2017). Yet, *C. elegans* gained prominence as a model system only later, emerging from foundational work in developmental biology and genetics, primarily based on mutagenesis approaches (Brenner 1974). By the year 2000, *C. elegans* had become a widely used study organism for several subfields, including the biology of aging. Rapid advances in aging research were driven by the discovery that mutations or other perturbations, such as germline ablation, could significantly extend lifespan in *C. elegans* (Klass 1983; Friedman and Johnson 1988; Kenyon *et al.* 1993; Apfeld and Kenyon 1999; Hsin and Kenyon 1999). However, the discovery of long-lived mutants opened a debate on a central topic in life history research: the "cost of reproduction" (Leroi 2001; Patel *et al.* 2002; Barnes and Partridge 2003; Box 2). Specifically, observations of lifespan extension with no apparent cost to fecundity or other forms of reproductive success challenged the presumed trade-off between reproductive vs somatic investment that is widely postulated within life history theory. This controversy was driven by differences in perspective between developmental geneticists and evolutionary biologists and the ever-present challenge of assessing ecologically relevant fitness traits in a laboratory setting.

In contrast to the long history of *Drosophila melanogaster* in evolutionary genetics (Powell 1997), evolutionary biologists only turned to *C. elegans* in the late 1990s, with the first mutation accumulation (MA) studies that quantified mutation rates and mutational variances for life history traits (Keightley and Caballero 1997; Davies *et al.* 1999; Vassilieva and Lynch 1999). However, the early molecular genetic insights into *C. elegans* lifespan and aging (Johnson and Wood 1982), as well as reproductive development (Hirsh *et al.* 1976; Sulston and Horvitz 1977; Kimble and Hirsh 1979) and the dauer diapause decision (Cassada and Russell 1975; Golden and Riddle 1982), established a foundation for understanding how life history traits might be genetically regulated. This foundation then offered mechanistic insight into observations of natural variation in life history made possible via wild isolate collections over the past few decades. Most recently, the accessibility of hundreds of whole-genome-sequenced wild strains (Cook *et al.* 2017; Crombie *et al.* 2024) has positioned *C. elegans* as a powerful model for statistical genetics and population genomics exploiting natural genetic and phenotypic variation (Andersen and Rockman 2022). Due to its reproductive mode of androdioecy, allowing for controlled manipulation of sex ratios and outcrossing, *C. elegans* has in addition become an attractive system for experimental evolution (Teotónio *et al.* 2017).

Box 2. *C. elegans* "aging genes" and the debate over the cost of reproduction

The negative relationship between reproductive success and survival is a pivotal life history trade-off and the lens through which life history evolution is often viewed. Several nonmutually exclusive arguments have been proposed to explain the trade-off between reproduction and lifespan. The disposable soma theory (Kirkwood 1977) describes the trade-off in physiological terms of resource allocation: investment into reproductive functions such as gonad development, gametogenesis, or mating efforts cannot simultaneously be invested in the maintenance of the soma, so reproductive expenditure necessarily limits expenditure toward longevity or survival. The theories of mutation accumulation (Medawar 1952) and antagonistic pleiotropy (Williams 1957) define the problem within the genetic context. Since environmental threats, such as predation or starvation, are likely frequent causes of mortality in the wild, mutations with deleterious effects late in life are partially shielded from purifying selection and may accumulate in a population. Mutations with late-age deleterious effects that are also pleiotropic, and promote fitness early in life by, for example, conferring a reproductive advantage, may be maintained in the population through positive selection. In both scenarios, the mutations induce senescence in long-lived individuals.

At the heart of these arguments lies the question of whether longevity is repressed directly through reproduction, and, if so, by which mechanisms. The advancement of experimental genetics broke open an access point to address this longstanding issue, in which *C. elegans* has played a starring role (Tatar 2023).

C. elegans became a leading system for research into the biology of aging with the discovery of lifespan-extending mutations. The first "aging gene", *age-1*, was discovered in *C. elegans* (Friedman and Johnson 1988), and kicked off a race to find others (Kenyon 2011). As mutations in these genes were found to extend lifespan, they were understood to promote aging in their wild-type functional state; this view established the concept of senescence as a genetic program rather than a stochastic process of decay (Kenyon 2005, 2011). Foremost among such genes were factors associated with insulin-like signaling, including positive regulators of dauer induction, *age-1* and *daf-2*, and the transcription factor *daf-16* (Friedman and Johnson 1988; Kenyon *et al.* 1993; Morris *et al.* 1996; Kimura *et al.* 1997; Lin *et al.* 1997; Henderson and Johnson 2001), and genes whose dysregulation extended or mediated lifespan in a *daf-16*-dependent manner (Tissenbaum and Guarente 2001; Vellai *et al.* 2003; Jia *et al.* 2004; Boehm and Slack 2005; Oh *et al.* 2005; Lehtinen *et al.* 2006; Shaw *et al.* 2007; Mouchiroud *et al.* 2013; Uno and Nishida 2016).

The findings that manipulating single genes can significantly extend lifespan were groundbreaking and garnered great interest in studying aging in molecular and developmental genetics. The discovery of so-called "aging or longevity genes" was seen as clear evidence of genetic control over aging, reflecting what many believed to be genetic programs for aging. While some genetic manipulations to extend lifespan exhibited clear costs to reproduction, like reduced brood size, others showed no obvious effects, or effects only under certain conditions. For example, *age-1* mutants exhibited no detectable reproductive deficit under standard laboratory conditions but were outcompeted by wild-type under nutritional stress (Walker *et al.* 2000). Other experiments revealed how distinct traits might be separably controlled: the highly pleiotropic *daf-2*, which is involved in dauer induction, reproduction, stress resistance, and aging, acts at different developmental time points (Dillin *et al.* 2002), and for genes required for larval development, RNAi knockdown in the adult can extend lifespan (Chen *et al.* 2007). These observations of lifespan extension without fixed costs to reproduction led to a debate over whether lifespan and reproductive success could be decoupled (Leroi 2001; Barnes and Partridge 2003; Kenyon 2005, 2011; Leroi *et al.* 2005; Partridge *et al.* 2005), which on its face appeared to challenge the central tenant of life history theory, the cost of reproduction.

However, principles of life history theory are rooted in trade-offs of fitness, which was not a defining concept in most of these studies. Most lifespan extensions in *C. elegans* occur after the reproductive phase, providing no fitness advantage; as a result, these long-lived phenotypes are invisible to natural selection. From an evolutionary perspective, any relevant trade-off between investment in somatic versus reproductive components occurs earlier in the life cycle, and experimentally induced, postreproductive lifespan extensions are secondary byproducts. That said, artificial extensions to lifespan were typically induced by null or hypomorphic alleles or simple overexpression constructs; if such laboratory-derived perturbations could truly decouple the cost of reproduction from longer lifespan, why does not natural selection tolerate, or even favor, such easy modifications? The answer, of course, is because perturbation of the wild-type, functional versions of these genes does come at a significant cost to fitness, which has been demonstrated in the right assays. For example, examination of age-specific rates of fecundity showed that *age-1* mutants exhibit increased reproductive success late in life but decreased fecundity early in life relative to wild-type (Maklakov *et al.* 2017), and competition experiments demonstrated that the reduced fecundity of the *daf-2* mutant, which occurs in early life, decreases fitness relative to wild type (Jenkins *et al.* 2004; Chen *et al.* 2007).

Another way to understand the debate is to recognize that the tension elides several issues. These researchers were asking distinct questions: whether increased longevity incurs a cost to reproduction; whether reproduction and longevity can be decoupled; and whether antagonistic pleiotropy is an explanation for aging.

If "cost" is defined as a phenomenon of resource allocation, the question is whether lifespan extensions occur by limiting reproduction. While the removal of germ cells had been shown to increase lifespan in diverse taxa, whether this occurred by a direct trade-off in resources was surprisingly difficult to determine (Braendle *et al.* 2011). However, seminal *C. elegans* experiments showed that the answer is largely "no". Ablation of the hermaphrodite larval germ precursor cells eliminates germline growth and reproduction and dramatically increases adult lifespan, yet ablation of the entire gonad, including both germ cells and somatic gonad precursors cells, does not (Kenyon *et al.* 1993; Hsin and Kenyon 1999). Moreover, inhibition of *C. elegans* reproduction by sterility mutants, mating assays, or chemicals, likewise does not extend lifespan (Gems and Riddle 1996; Hsin and Kenyon 1999; Leroi 2001). These results emphasize the importance of understanding the functional architecture of trade-offs and the fallacy of inferring causality underlying trait correlations (Houle 1991; Rose and Bradley 1998; Leroi 2001; Barnes and Partridge 2003; Flatt and Heyland 2011; Hughes and Leips 2016). They also demonstrate that reproduction and longevity can be decoupled in the proximate sense, under specific conditions.

However, the question of whether antagonistic pleiotropy is an explanation for aging is embedded in a broader evolutionary context. In *D. melanogaster* and other systems with an early history of studying natural variation from wild populations, observations of genetic and phenotypic correlations among traits—namely, the negative correlation between lifespan and fecundity and a positive correlation between lifespan and other determinants of survival, like stress tolerance—motivated hypotheses about adaptive life history evolution with antagonistic pleiotropy as a driving mechanism (Rose *et al.* 1992; Schmidt *et al.* 2005; Paaby and Schmidt 2009). Such observations have rarely been a focus in *C. elegans* research, although the role of stress resistance as an intimate component of aging biology is apparent by the persistent connection between lifespan extension and the dauer decision; the same genes regulate both. In challenging environments, *C. elegans* lifespan extension routinely exhibits costs to reproductive output and fitness, to the point that the presumptive long-lived mutant may be outlived by the wild-type (Walker *et al.* 2000; Savory *et al.* 2014; Briga and Verhulst 2015). This ultimate relationship strongly appears to be governed by pleiotropy, in part because both reproduction and persistence (including dauer induction) are mediated by the same insulin-like hormones that produce incompatible physiologies (Tatar 2023). Furthermore, the common role of insulin-like signaling in mediating life history phenotypes across taxa suggests that antagonistic pleiotropy is ubiquitous, as the accumulation of random mutations would not likely produce conserved mechanisms (Austad and Hoffman 2018).

Box 2. (Continued)

In sum, from an evolutionary perspective, the question that presupposes whether a trade-off can be broken is whether ecologically relevant fitness traits can be adequately assessed in the laboratory. An observation of lifespan extension with no apparent cost to reproduction in the lab does not mean there is not a cost in nature, and such observations are not evidence against antagonistic pleiotropy; they are simply not arguments for it. Moreover, the relevant trait is always fitness, a concept that requires context. For *C. elegans*, which likely colonizes ephemeral food sources with bursts of clone-like subpopulations, programmed senescence may actually increase fitness for the genotype by group selection (Lohr *et al.* 2019; Galimov and Gems 2020; Chapman *et al.* 2024). Investigations that have evaluated long-lived *C. elegans* mutants over multiple generations or in challenging environments have consistently observed a loss of fitness relative to wild-type, but experimental tests of evolutionary hypotheses often require assays that are highly sensitive, relatively naturalistic, or both (Briga and Verhulst 2015; Austad and Hoffman 2018).

During the past 25 years, studies of wild isolates and sampling efforts across diverse environments have begun to elucidate the evolutionary ecological context of *C. elegans* and related *Caenorhabditis* nematodes. Key observations include the predominance of the dauer stage in wild populations, as well as the existence of 2 alternative mating systems within the genus, gonochoristic and androdioecious, and the predominance of selfing in the latter (Kiontke 2006; Félix and Braendle 2010; Cutter 2015; Frezal and Félix 2015; Schulenburg and Félix 2017; Ben-David *et al.* 2021; Lee *et al.* 2021; Noble, Yuen *et al.* 2021). The discovery of more than 70 new *Caenorhabditis* species, up from only 10 species in culture in 2005 (Kiontke 2006), together with their sequenced genomes and now well-resolved phylogeny (Kiontke, Félix *et al.* 2011; Stevens *et al.* 2019; Dayi *et al.* 2021), has accelerated opportunities for comparative studies. Prevailing research topics include the repeated evolutionary transition from outcrossing to selfing modes of reproduction within *Caenorhabditis* (Kiontke, Félix *et al.* 2011) and, among more distant relatives of *C. elegans* across Nematoda and beyond, transitions between free-living and parasitic life styles (Blaxter and Koutsovoulos 2014).

Scope of this review

We provide an overview of what is known about the *C. elegans* life cycle and life history, discussing specific examples with an emphasis on reproductive life history and trade-offs, their underlying genetic mechanisms, environmental sensitivity, and natural variation within *C. elegans*. We further briefly review nematode life history within a broader phylogenetic context by discussing the evolution of specific life history features in the genus *Caenorhabditis* and major life cycle transitions in the phylum Nematoda. Some life history topics are not discussed extensively here because they are the subjects of several recent *Wormbook* articles and other reviews, including plasticity in response to nutrient availability (Baugh and Hu 2020), mating systems, and sexual selection (Cutter *et al.* 2019), reproductive system evolution across nematodes (Haag *et al.* 2018), and experimental evolution (Teotónio *et al.* 2017). We also do not exhaustively discuss the extensive literature on *C. elegans* aging and lifespan, for which many recent reviews already exist (Mack *et al.* 2018; Bayersdorf and Schumacher 2019; Zhang *et al.* 2020; Scharf *et al.* 2021). Our aim here is to complement these existing works by integrating findings from both molecular genetics and evolutionary ecological research on *C. elegans* to address what is known about its life history and what we can learn about life history traits, their genetics, and evolution using *Caenorhabditis* nematodes.

Overview of *C. elegans* life history

Life cycle

C. elegans exhibits androdioecy (Fig. 1), with both hermaphrodites and males coexisting. It evolved from a dioecious (or gonochoristic) ancestor that had separate sexes for male and female modes of reproduction (Kiontke and Fitch 2005; Kiontke, Félix *et al.* 2011). Hermaphrodites closely resemble females of dioecious *Caenorhabditis* species, and male function is largely limited to a transient period of spermatogenesis; hermaphrodites cannot cross-fertilize (Hirsh *et al.* 1976; Ward and Carrel 1979). However, hermaphrodite self-fertilization (selfing) is the dominant mode of reproduction, and males are rare under standard laboratory conditions and in natural populations (Hodgkin and Doniach 1997; Barrière and Félix 2005a; Teotónio *et al.* 2006; Rockman and Kruglyak 2009; Andersen *et al.* 2012; Richaud *et al.* 2018; Lee *et al.* 2021; Lim *et al.* 2021). Within *Caenorhabditis*, androdioecy has evolved independently at least three times: *C. elegans*, *C. briggsae*, and *C. tropicalis* are all partial selfers with outcrossing ancestors (Kiontke and Fitch 2005; Kiontke, Félix *et al.* 2011; Stevens *et al.* 2019). This transition in life history strategy has significant consequences for demography and population genetics and has been a central focus of life history research in its own right.

C. elegans developmental time is rapid (Brenner 1974; Byerly *et al.* 1976) and selfing hermaphrodites can produce hundreds of offspring but cross-fertilization can more than double lifetime production (Mendenhall *et al.* 2011). Typically, larger male sperm consistently outcompete the smaller hermaphrodite sperm; and as a consequence, resulting cross-progeny displays a sex ratio approaching 1:1 (Ward and Carrel 1979; LaMunyon and Ward 1998; Cutter *et al.* 2019). A key feature of the *C. elegans* life cycle is the adaptive, plastic response of larval phenotypes to environmental cues (Fig. 1; Baugh and Hu 2020). Under high population density, high temperature, or low food concentration, larvae develop into an alternative third larval stage called *dauer*, a form of diapause, common in diverse free-living nematode taxa of the suborder *Rhabditina* (Cassada and Russell 1975; Ley 2006). Developmentally arrested dauers are capable of surviving several months in the absence of food (Cassada and Russell 1975), are highly stress-resistant, and reflect the key dispersal stage of *Caenorhabditis* nematodes (Frezal and Félix 2015). As soon as environmental conditions improve, larvae rapidly exit the dauer stage and resume reproductive development. *C. elegans* dauer production thus allows for environmentally cued developmental decisions to reschedule the reproduction and survival trajectories in stressful environments. We will discuss dauer formation, and other phenomena of *C. elegans* life history plasticity, in more detail in several sections of this review.

Ecology

C. elegans is a globally distributed, free-living microbivore and has been isolated from diverse habitats and substrates, primarily rotting plant matter such as fruits, flowers, plant stems, leaves, compost, or invertebrates associated with these substrates (Félix and Braendle 2010; Andersen *et al.* 2012; Frezal and Félix 2015; Schulenburg and Félix 2017; Lee *et al.* 2021). Given the absence of an apparent specificity for substrates or phoretic (dispersal)

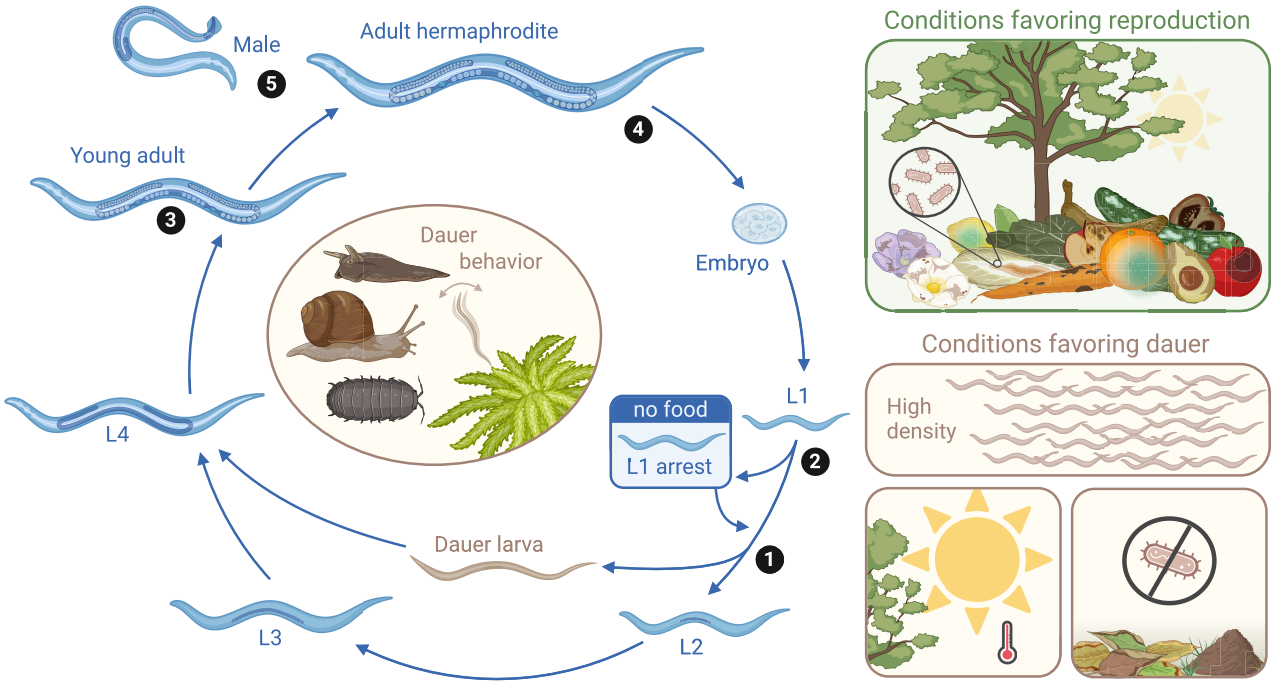

Fig. 1. Key life history trade-offs in *C. elegans* life cycle and ecology. The *C. elegans* life cycle includes 4 larval stages (L1–L4), and egg to adult development time is ~3.5 days in optimal conditions at 20°C. However, under stressful conditions, individuals can enter the alternative dauer larval state and persist for several months without food. In dauer, dispersal by phoretic associations with invertebrate carriers is facilitated by nictation, in which individuals or cooperative aggregates wave from a high point on the substrate, such as the tip of a moss leaf. The dauer decision (1) represents a key trade-off in *C. elegans* life history because investment in reproduction via the direct developmental trajectory comes at a potential cost to survival or migration to a more favorable environment, and vice versa (described in Box 3). (2) Other trade-offs include the option to temporarily arrest at the L1 larval stage, (3) the investment in spermatogenesis vs oogenesis during reproductive maturation (illustrated in Fig. 2), and (4) the degree of egg retention, which can lead to matricidal hatching (described in Box 4). The *C. elegans* mating system consists of XX hermaphrodites and XO males; males result from nondisjunction of the X chromosomes at meiosis or as descendants from crosses between hermaphrodites and males. The sex ratio (5) also reflects a trade-off, as it affects the rates of the alternative modes of outcrossing vs selfing. The evolution of hermaphrodite sex determination and the androdioecious mating system represents a major life history transition for *C. elegans*, *C. briggsae*, and *C. tropicalis*, all of which evolved from outcrossing ancestors. Created with BioRender.com.

associations, *C. elegans* can be considered a generalist, colonizing a wide range of ecological niches (Félix and Braendle 2010; Li *et al.* 2014). *C. elegans* occupies a variety of thermal niches, yet it is notably absent or confined to high-altitude environments in tropical regions with elevated temperatures (Evans *et al.* 2017; Lee *et al.* 2021). This observation is consistent with reports that *C. elegans*, largely independent of geographic origin, shows optimal growth at around 20°C and reproduction becomes compromised at rearing temperatures above 25°C (Félix and Duveau 2012; Petrella 2014; Poullet *et al.* 2015; Evans *et al.* 2017; Frézal *et al.* 2018).

C. elegans exhibits a dynamic boom-and-bust lifestyle linked to substrates that are generally highly ephemeral, occurring mostly in the form of dauers interrupted by short reproductive phases until food exhaustion on a given substrate (Félix and Duveau 2012; Schulenburg and Félix 2017). This model implies that rapid population size expansion on rotting substrates is followed by strong population bottlenecks, frequent extinction, and recolonization events, mainly through the dispersing dauer stage (Félix and Braendle 2010; Frezal and Félix 2015). Surveys of natural populations confirm this idea of temporally and spatially fluctuating metapopulation dynamics with recurrent, often seasonal bottlenecks (Barrière and Fèlix 2005b, 2007; Haber *et al.* 2005; Félix and Duveau 2012; Petersen *et al.* 2015; Richaud *et al.* 2018). The boom-and-bust cycle and associated metapopulation dynamics, together with the consequences of predominant selfing and recent selective sweeps, are key features determining population structure and genetic diversity; their understanding is also essential to better understand the "real" *C. elegans* life cycle and to identify the most pertinent life history traits to study in the laboratory.

An idiosyncratic reproductive system: androdioecy

Androdioecy is rare, both in animals and plants, and *C. elegans*' protandrous form of sequential, self-fertile hermaphroditism is rarer still (Pannell 2002; Weeks *et al.* 2006; Leonard 2019). This sequential production of sperm and oocytes has been revealed to underlie a key trade-off, and an especially elegant example of life history articulated at the genetic, organismal, and population levels. During germ cell development, the transition from sperm too oocyte production is irreversible (Ellis 2010, 2022), hence the number of sperm cells ultimately limits self-fecundity (Ward and Carrel 1979; Hodgkin and Barnes 1991; Singson 2001; Cutter 2004). This is unlike most other organisms, where the production of larger female gametes typically limits fecundity (Bateman 1948; Charnov 1982). However, it is generally thought that increasing sperm production delays reproductive maturity (Hodgkin and Barnes 1991; Barker 1992; Cutter 2004; Chasnov 2011; Murray and Cutter 2011), such that the sperm-oocyte switch governs the optimization of either generation time or lifetime fecundity under selfing (Fig. 2).

The evolution of androdioecy and the primary selfing mode of reproduction has substantially shaped the demography and population genetics of *C. elegans*, *C. briggsae*, and *C. tropicalis*.

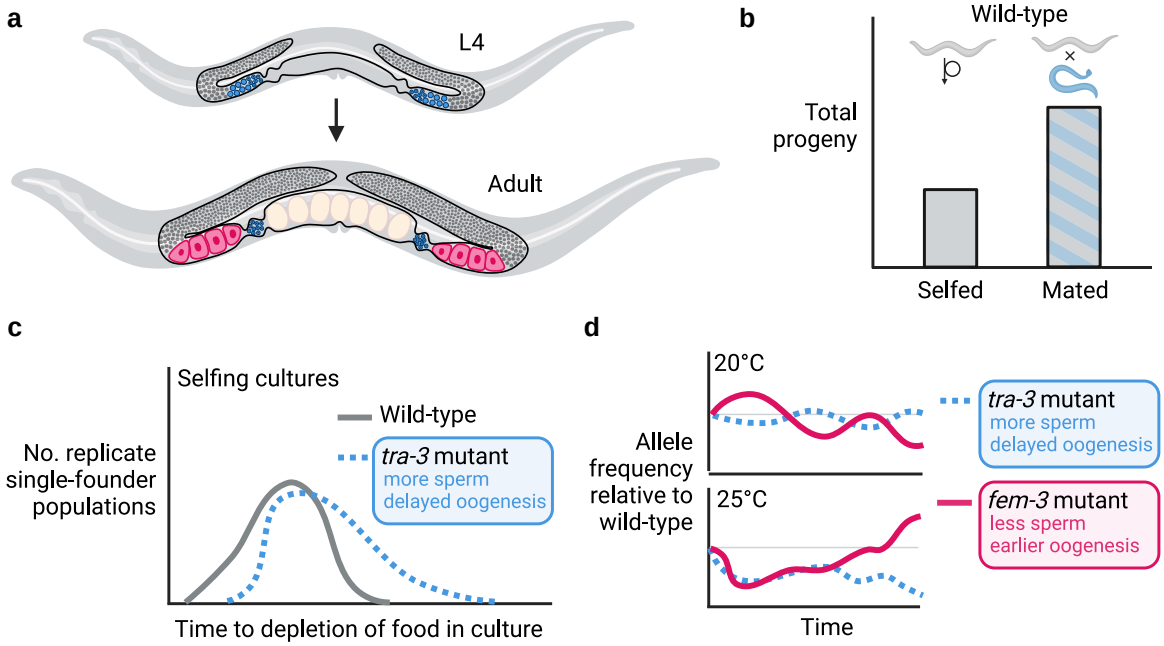

Fig. 2. Sequential hermaphroditism confers a trade-off between growth rate and reproduction. a) During the L4 stage of hermaphrodite larval development, germ cell progenitors (gray) undergo spermatogenesis (blue), then transition irreversibly to oogenesis (red). b) Consequently, the number of sperm cells is fixed in the reproductively mature hermaphrodite, though oocytes continue to be produced throughout adulthood. In optimal laboratory conditions, an exclusively self-fertilizing hermaphrodite produces ~250–350 sperm and the same number of lifetime self-progeny. In contrast, a mated hermaphrodite may produce up to 500–1,000 offspring with sperm from the inseminating male, approximately double the lifetime reproductive success. c) However, relative to a mutant with prolonged hermaphrodite sperm production and higher lifetime self-fecundity, the wild-type genotype begins oogenesis sooner, begins egg-laying sooner, and exhibits faster population growth, as measured by time to food depletion (Hodgkin and Barnes 1991). d) Consequently, the delay to oocyte production and reproductive maturation decreases fitness in an environment of resource exploitation, and theoretical work demonstrates that growth rates under selfing are maximized by producing intermediate levels of sperm (Barker 1992; Cutter 2004; Chasnov 2011). Sperm number in the *C. elegans* hermaphrodite is likely under strong selection to optimize this fitness trade-off, though experimental evolution manipulating sperm count over different environmental conditions shows that the optimal sperm number is context dependent (Murray and Cutter 2011). Created with BioRender.com.

While outcrossing species exhibit high rates of heterozygosity and inbreeding depression (Dolgin *et al.* 2007; Barrière *et al.* 2009; Dey *et al.* 2012, 2013; Cutter *et al.* 2019; Teterina *et al.* 2023), these naturally inbred species persist as homozygous clonal lineages, with rare interbreeding (Richaud *et al.* 2018; Cutter *et al.* 2019), dramatically greater capacity for dispersal, and broader geographic ranges (Kiontke, Félix *et al.* 2011; Frezal and Félix 2015; Thomas *et al.* 2015; Stevens *et al.* 2019; Noble, Yuen *et al.* 2021). Likely arising from its ability to self, which facilitates both dispersal and subsequent boom-and-bust cycles, *C. elegans* exhibits chromosome-level selective sweeps, which explains its low genetic diversity and strong linkage disequilibrium relative to outcrossing species (Cutter and Payseur 2003; Barrière and Félix 2005b; Cutter 2006; Rockman *et al.* 2010; Andersen *et al.* 2012; Lee *et al.* 2021). However, as the evolution of selfing has shaped the population genetics of *C. elegans*, it has presumably also facilitated adaptive life history evolution as this generalist species has colonized new habitats (Crombie *et al.* 2019; Lee *et al.* 2019, 2021; Zhang *et al.* 2021).

Though all organisms are idiosyncratic, we note that androdioecy—and its biological consequences—can limit the application of *C. elegans* to some questions. This may be particularly true for life history theory developed for obligately sexual organisms (Roff 1992; Stearns 1992). Therefore, some theoretical assumptions may not apply to, or be straightforwardly testable in, *C. elegans*. For example, selfing influences the rate of inbreeding depression, which in turn can affect correlations among traits like the trade-offs predicted by aging theory (Carvalho *et al.* 2014; Teotónio *et al.* 2017; Lesaffre and Billiard 2019). Additionally, life history theory on how hermaphrodites optimally allocate resources toward male vs female function (sex allocation) is not easily applicable to *C. elegans* as most of this work has focused on simultaneous, rather than sequential, hermaphrodites (Charnov 1982; Munday *et al.* 2006; Schärer 2009; Hitchcock and Gardner 2023).

On the other hand, the androdioecious reproductive system offers experimentalists exceptional utility for investigating life history topics that are challenging to explore in other organisms. Facultative outcrossing and easy genetic transformation of *C. elegans* hermaphrodites into females allows the experimental manipulation of reproductive mode and sex ratios. This has been a focus of experimental evolution studies, which we touch upon briefly below and which is treated extensively in the Wormbook chapter "Experimental Evolution with *Caenorhabditis* Nematodes" (Teotónio *et al.* 2017). The fact that *C. elegans* strains are nearly completely isogenic is especially practical, for life history research and beyond: they suffer no inbreeding depression (Cutter *et al.* 2019); are ideally suited for classical forward and reverse genetics approaches, as exemplified by the groundbreaking research in aging; are likewise highly amenable to contemporary methodologies including high throughput phenotyping, RNA interference, and gene editing and genome engineering (Dickinson and Goldstein 2016; Doitsidou *et al.* 2016; Azorsa and Arora 2018; Nance and Frøkjær-Jensen 2019; Le *et al.* 2020); and are optimized for studying phenotypic plasticity across different environments, an essential feature of life history. *C. elegans* natural homozygosity likewise aids in trait mapping, though selfing also induces strong linkage disequilibrium that impedes the ability to fine-map variants by association using wild strains (Rockman *et al.* 2010; Andersen and Rockman 2022).

Finally, we also note that the independent evolution of androdioecy in *C. elegans*, *C. briggsae*, and *C. tropicalis* offers an attractive opportunity to dissect the evolutionary transitions of reproductive modes, which we only briefly address below. We direct the reader to the Wormbook chapter "Males, Outcrossing, and Sexual Selection in *Caenorhabditis* Nematodes" (Cutter *et al.* 2019). This review describes comparative insights gained from the repeated evolution of androdioecy from a gonochoristic ancestor; it also includes an in-depth treatment of the genetic dissection of the *C. elegans* sex determination system and how its experimental manipulation facilitates highly precise tests regarding mating system variation and the role of males. The Wormbook chapter "From 'the Worm' to the 'Worms' and Back Again: The Evolutionary Developmental Biology of Nematodes" (Haag *et al.* 2018) also reviews the genetics of sex determination within the genus *Caenorhabditis* and the repeated evolution of hermaphroditism.

Phenotypic plasticity of life history traits

Phenotypic plasticity describes the influence of the environment in altering organismal development and phenotypic outcomes (West-Eberhard 2003). Specifically, phenotypic plasticity is the ability of a genotype to generate phenotypic variation in response to variation in the environment, including across generations (e.g. maternal effects). As life history traits tend to show strong environmental sensitivity (Price and Schluter 1991; Houle 1992; Acasuso-Rivero *et al.* 2019), plasticity is a central concept in life history evolution, relevant to the efficacy of natural selection and rates of phenotypic evolution (Via and Lande 1985, 1987; West-Eberhard 1986, 1989; Gillespie and Turelli 1989; Price *et al.* 2003). However, phenotypic plasticity may reflect both adaptive and nonadaptive responses.

C. elegans developmental progression, life cycle decisions, and quantitative life history traits such as fecundity and lifespan are strongly contingent on environmental context, both biotic and abiotic (Braendle *et al.* 2008; Schulenburg and Félix 2017; Baugh and Hu 2020). Here, we focus on the plastic responses that have been characterized in *C. elegans* with respect to dauer induction, nutritional availability, and observations of transgenerational plastic responses.

The dauer decision

The dauer decision is a critical point in the *C. elegans* life cycle (Fig. 1) and reflects a clear example of a polyphenism: a plastic response giving rise to distinct phenotypes with alternative morphologies and life histories (Mayr 1963; Moran 1992; Nijhout 2003). The decision point occurs in the first larval stage and development either proceeds toward reproductive maturity or begins differentiation into dauer; the alternative trajectories represent either investment in immediate reproduction or somatic maintenance and dispersal.

The dauer larva possesses morphological and metabolic adaptations that confer resistance to various environmental stressors, including prolonged starvation, desiccation, and extreme temperatures (Cassada and Russell 1975; Klass and Hirsh 1976; Hu 2007; Baugh and Hu 2020). As in many other free-living nematodes, the dauer stage is the central dispersal stage, and dauer larvae engage in a specialized waving behavior called nictation to form phoretic associations with invertebrate carriers (Cassada and Russell 1975; Lee *et al.* 2012). In nature, *C. elegans* likely persists predominantly in the nonreproductive dauer stage, with reproductive development occurring during brief, potentially seasonally delineated periods when populations can proliferate on ephemeral food sources.

The *C. elegans* dauer decision is distinguished by its exceptionally thorough genetic characterization, rendering it one of the best-characterized polyphenisms in animals (Hu 2007; Fielenbach and Antebi 2008; Baugh and Hu 2020). Dauer induction is triggered by small-molecule pheromones (ascarosides) and environmental signals such as food type and quantity or temperature, perceived by both the external sensory system and internal sensing of nutritional status; dauer exit and reentry into reproductive development occur when encountering conditions of increased food levels, low pheromone, and low temperature (McGrath *et al.* 2011; Neal *et al.* 2015; O'Donnell *et al.* 2018). Integration of these sensory and endocrine signals occurs through evolutionarily conserved pathways, including-β and insulin-like signaling (Fielenbach and Antebi 2008; Antebi 2013). Ultimately, the regulation of dafachronic acids (DAs), bile acid-like steroid hormones, acts as the central switch between alternative life cycles (Gerisch *et al.* 2001, 2007; Motola *et al.* 2006; Baugh and Hu 2020). For a detailed discussion of the genetics controlling dauer regulation in *C. elegans*, we direct interested readers to the reviews by Hu (2007), Fielenbach and Antebi (2008), and Baugh and Hu (2020).

Responses to nutritional availability

C. elegans life history exhibits pronounced plasticity in response to variation in nutritional availability even beyond the central dauer switch (Baugh and Hu 2020; Mata-Cabana *et al.* 2021; Rashid *et al.* 2021). For example, newly hatched larvae in food-scarce environments may pause development at the L1 stage and undergo metabolic changes that enhance stress resistance. This arrest enables larvae to endure for days to weeks before resuming development upon feeding (Baugh and Hu 2020; Jordan *et al.* 2023). Acute starvation also induces developmental arrest at later stages, and starvation in late larvae or adults leads to marked changes in reproductive physiology and a reversible quiescent state, sometimes termed adult reproductive diapause (ARD) (Angelo and Van Gilst 2009; Seidel and Kimble 2011; Schindler *et al.* 2014; Gerisch *et al.* 2020).

Moreover, intermittent starvation and milder forms of nutrient stress during larval development will significantly affect many life history traits expressed later in life, including body size, reproductive success, and lifespan (Jobson *et al.* 2015; Webster *et al.* 2022; Jordan *et al.* 2023). Similarly, passage through the dauer stage may modulate germline and somatic development, leading to changes in adult reproductive life history (Kim and Paik 2008; Ow *et al.* 2018, 2021; Webster *et al.* 2018). The extent to which plasticity in these life history phenotypes represents an adaptive response remains often unclear. However, the mechanisms coordinating nutrient availability, developmental progression, and quiescence involve shared nutrient-sensing and metabolic processes through conserved signaling pathways, including target of rapamycin insulin-like, and nuclear hormone receptor (NHR) signaling (Antebi 2013; Baugh and Hu 2020). Taken together, this research underlines the presence of extensive plasticity of *C. elegans* development and reproduction in response to the environment, and how specific environmental factors can instruct developmental decisions. This research also highlights that the *C. elegans* germline is remarkably plastic—in contrast to the stereotyped, near-invariant somatic lineage—and exhibits changes in germ cell proliferation, meiotic progression, timing of the sperm-oocyte switch, and apoptosis and quiescence in response to environmental variation (Korta and Hubbard 2010; Pekar *et al.* 2017; Hubbard and Schedl 2019; Baugh and Hu 2020; Fausett

et al. 2021; Aprison, Dzitoyeva, Angeles-Albores *et al.* 2022; Aprison, Dzitoyeva, Ruvinsky 2022).

Nutritional cues further influence a multitude of acute *C. elegans* behaviors (Bargmann 2006). Starvation and low food quality, for example, inhibit egg-laying activity in *C. elegans*, leading to egg retention (bagging) and, ultimately, to the hatching of larvae within the uterus (Maupas 1900; Chen and Caswell-Chen 2003). This phenomenon of environmentally induced matricidal hatching in stressful environments potentially represents a mechanism of maternal resource provisioning (Chen and Caswell-Chen 2003, 2004) or maternal protection (Vigne *et al.* 2021; Mignerot *et al.* 2024).

Responses to the microbial and chemical environment

In addition to food availability and quantity, *C. elegans* development, metabolism, and life history are sensitive to variations in the type and composition of microbial food source provided (Schulenburg and Félix 2017). Changing the typical laboratory diet of *Escherichia coli* (strain OP50) to other bacteria, including bacteria naturally associated with *C. elegans*, has diverse effects, ranging from highly deleterious pathogenic effects to more subtle quantitative effects that modify suites of life history traits (Samuel *et al.* 2016; Schulenburg and Félix 2017; Zhang *et al.* 2017; Dirksen *et al.* 2020). Various taxon-specific bacterial metabolites have been identified that alter diverse life history traits, such as age at maturity and lifetime reproductive success (Virk *et al.* 2012; Gusarov *et al.* 2013; MacNeil *et al.* 2013; Watson *et al.* 2014). In several cases, the perception of bacterial diets through olfactory neurons alone can prove substantial enough to significantly modify the reproductive life history of *C. elegans* (Sowa *et al.* 2015; Mishra *et al.* 2023) as well as lifespan (Maier *et al.* 2010).

Signaling via neuronal perception of chemical stimuli also modulates *C. elegans* life history in response to interactions with conspecifics. Pheromonal communication via secreted small molecules such as ascarosides plays diverse roles in inducing various life history responses (Ludewig 2013; Park et al. 2019). For example, population-density-related levels of these signaling molecules both guide the dauer decision and modulate the speed of hermaphrodite reproductive development and onset of maturity (Ludewig *et al.* 2017, 2019; Perez *et al.* 2021). In addition, male pheromone signals can alter diverse aspects of hermaphrodite reproductive physiology, with the potential to confer both presumed costs and benefits for alternative life history traits (Wong *et al.* 2020; Aprison, Dzitoyeva, Angeles-Albores *et al.* 2022; Angeles-Albores *et al.* 2023).

Plastic responses across generations

The effect of the environment on *C. elegans* life history traits may persist across generations (Perez and Lehner 2019; Baugh and Day 2020). Factors such as osmotic stress, hypoxia, starvation, exposure to pathogens, and maternal physiology and age can modify offspring life history traits as maternal or grandmaternal effects (Dey *et al.* 2016; Baugh and Day 2020; Burton *et al.* 2020, 2021; Perez *et al.* 2021). For example, starvation or dietary restriction will cause hermaphrodites to produce larger (but fewer) embryos, suggestive of enhanced offspring provisioning under nutrient stress (Harvey and Orbidans 2011; Hibshman *et al.* 2016). This effect is mediated by insulin-like signaling to upregulate vitellogenin (yolk) provisioning of oocytes in response to nutrient stress and may be adaptive, as offspring exhibit improved starvation resistance, developmental integrity, and reproductive success (Hibshman *et al.* 2016; Jordan *et al.* 2019). This phenomenon is further modulated by maternal age in the absence of dietary restriction (Perez *et al.* 2017), an indication, along with other studies on *C. elegans* reproductive aging (Luo and Murphy 2011; Scharf *et al.* 2021), that maternal age itself can influence offspring quality independently of changes in the external environment. Maternal effects may be especially likely to evolve in fluctuating environments (Dey *et al.* 2016); the environment and cues about it in the maternal generation shape the type of maternal effect that can evolve (Proulx and Teotónio 2017).

Beyond maternal (and grandmaternal) effects, *C. elegans* exhibits evidence of plastic responses persisting transgenerationally, over 3 or more generations. Work in *C. elegans* has been groundbreaking in elucidating mechanisms of transgenerational epigenetic inheritance, with especially significant characterization of the role of small RNAs in mediating gene expression and germline function (Perez and Lehner 2019; Baugh and Day 2020). However, for the field of life history evolution, the outstanding question is whether transgenerational epigenetic inheritance plays a role in plastic responses that are both environmentally induced and adaptive. For adaptive plasticity to evolve as a transgenerational response, conditions likely require fluctuating environmental factors that would favor an anticipatory response, which theory and experimental evolution support in *C. elegans* (Dey *et al.* 2016; Proulx and Teotónio 2017; Proulx *et al.* 2019).

The genetic basis of life history variation

As with all traits, the evolution of diverse life history strategies arises from heritable variation in the wild (Fisher 1930; Roff 1992; Stearns 1992; Falconer and Mackay 1996; Walsh and Lynch 2018). While elucidating the genetic basis of intraspecific trait variation is a central aim of evolutionary genetics in general (Walsh and Lynch 2018), this pursuit can be especially challenging for life history traits, for several reasons: (1) as described above, life history traits may be especially plastic in the face of environmental variation, leading to extensive phenotypic variation in the absence of genetic differences; (2) life history traits may be more likely to be polygenic, with potentially many genetic variants each contributing small effects; and (3) such complex traits are also frequently influenced by interactions within and between genetic loci (dominance and epistasis), by the dependency between alleles and the external environment (genotype-by-environment interactions, GxE), and by stochastic processes (Houle 1992; Walsh and Lynch 2018).

C. elegans research has substantially advanced our understanding of the genetic basis of variation in reproductive phenotypes, longevity, developmental timing, and other life history traits, especially in the last decade with the accessibility of hundreds of whole-genome-sequenced wild strains (Crombie *et al.* 2024). *C. elegans* exhibits heritable phenotypic variation in essentially every trait that has been measured, providing rich opportunity to examine the ecological, physiological, and molecular genetic aspects of life history variation in a well-established developmental model system.

Heritable variation is observed when wild genotypes, reared in the lab under the same conditions, exhibit phenotypic differences. Many studies have sought to uncover the genetic basis for this variation, either by mapping the causal regions, potentially to the nucleotide level, or by revealing the nature of genetic architecture more generally, such as the number of contributing variants and their dependence on each other or on the environment in trait expression. In this section, we describe what we know about the genetic basis of life history variation, first by detailing what we

have learned over the evolution of quantitative genetic approaches, then by summarizing insights about the complex genetic architecture of life history components. We conclude by summarizing insights gleaned from 2 related endeavors, experimental evolution and the study of laboratory adaptation.

Lessons learned from early quantitative analyses of life history variation

C. elegans researchers aiming to uncover genetic determinants of lifespan were among the first to investigate the genetic basis of natural variation in *C. elegans*, and conducted the first quantitative trait locus (QTL) analysis (Johnson and Wood 1982). This study indicated that lifespan has a heritable, genetic component, and other early mapping experiments pursuing lifespan simultaneously considered related life history traits including development rate, aspects of fertility and fecundity, age of sexual maturation, and population growth rate, all of which exhibited natural genetic variation (Ebert *et al.* 1993; Johnson and Hutchinson 1993; Brooks *et al.* 1994; Shook *et al.* 1996; Shook and Johnson 1999). These approaches employed linkage analysis to identify genomic regions contributing to phenotypic differences, or QTL, between 2 strains; in these early studies, the strains were the reference strain N2 and the "Bergerac" strain BO. Linkage analysis is performed by phenotyping an established set of recombinant inbred lines, or RILs, derived from the F2 generation of the parental cross [for comprehensive primer on linkage mapping and other mapping approaches in *C. elegans*, we direct the reader to Andersen and Rockman (2022)]. While these studies paved the way for quantitative genetic studies in *C. elegans*, their significance was limited as the BO strain from Bergerac is a mutator strain, with an unusually high copy number of *Tc1* transposons and strong genetic and phenotypic instability (Gaertner and Phillips 2010; Daigle *et al.* 2022).

Subsequent quantitative trait analyses in *C. elegans* were heavily based on mapping panels derived from N2 and the genetically divergent Hawaiian strain CB4856, which enabled the mapping of numerous life history traits including fecundity, growth rate, body size, dauer formation, and lifespan (Gutteling, Doroszuk *et al.* 2007; Gutteling, Riksen *et al.* 2007; Rodriguez *et al.* 2012; Green *et al.* 2013, 2014; Andersen *et al.* 2014, 2015; Stastna *et al.* 2015; Zhu *et al.* 2015). The large number of strains and the randomized distribution of variants at intermediate frequency within panels offered improved power for mapping life history traits, which can be labor-intensive to measure or sensitive to environmental variation (Andersen and Rockman 2022). However, some of the most dramatic life history differences between N2 and CB4856 have been explained by highly pleiotropic effects of N2-specific alleles in several genes (e.g. *npr-1*, *glb-5*, *nath-10*) (McGrath *et al.* 2009; Duveau and Félix 2012; Andersen *et al.* 2014; Sterken *et al.* 2015; Evans *et al.* 2021). These likely arose in the N2 lineage under long-term adaptation to laboratory settings, as we describe in more detail below.

Improved trait mapping through natural genetic diversity

The availability of newly isolated wild strains, including strains with increasingly divergent genomes (Cook *et al.* 2017; Crombie *et al.* 2024), significantly advanced mapping opportunities by making it possible to perform genome-wide association analyses and construct more advanced mapping resources, including panels derived from multiple parents (Andersen and Rockman 2022). They also allowed a wider scope of intraspecific variation to be surveyed. Unlike linkage mapping, which operates on variation derived from crosses in the laboratory, usually between 2 strains, genome-wide association mapping is performed on a collection of wild strains. *C. elegans* confers both advantages and disadvantages in association mapping: as strains are naturally isogenic and homozygous, they are easily replicated without inbreeding depression, an advantage over many other metazoan systems (Lynch and Walsh 1998 ; Charlesworth and Willis 2009). On the other hand, the strong linkage disequilibrium arising from the predominance of selfing in the wild impedes fine-scale resolution of causal regions (Rockman *et al.* 2010; Andersen and Rockman 2022; Widmayer *et al.* 2022), so identification of specific variants requires following association analyses with labor-intensive candidate gene and introgression efforts (Andersen and Rockman 2022). One recent study (Zhang *et al.* 2021) evaluated natural variation in fecundity in over 100 strains and showed that the associated genomic regions correlate with chromosome-scale selective sweeps that shape the global *C. elegans* population structure. This important finding suggests that the historically recent and rapid expansion of *C. elegans* across the globe involved marked changes in life history, likely linked to adaptive changes in reproductive development to optimally exploit novel, substrate-rich habitats of predominantly human-associated habitats (Crombie *et al.* 2019; Lee, Zdraljevic, Cook *et al.* 2019; Lee, Zdraljevic, Stevens *et al.* 2021; Zhang *et al.* 2021).

From QTL to QTV

For researchers studying the genetic basis of natural variation, the gold standard has always been to identify the causal mutations at the nucleotide level. There has also been a persistent call to open up the "black box" of molecular, developmental, and physiological mechanisms that underlie the proximal regulatory mechanisms governing life history variation (Riska 1989; Leroi 2001; Roff 2007; Flatt and Heyland 2011). Given its dominance in molecular and developmental genetics, *C. elegans* offers valuable access, and one point of entry is to resolve the mapped genomic regions down to the quantitative trait variants (QTVs). The availability of the wild strain collections and the advances in quantitative genetic approaches have made this a realistic goal for many studies, typically achieved by isolating putative subregions in near-isogenic lines (NILs) and transgenic validation of the candidate molecular variants (Evans *et al.* 2021). Diverse QTV for life history attributes including dauer induction, fecundity and competitive fitness, and growth and body size have now been identified (Evans *et al.* 2021). We describe 2 exemplars of QTV mediating life history, the propensity to enter dauer (Box 3) and changes in egg-laying behavior that underlie constitutive matricidal hatching (Box 4).

However, even as studies like these offer valuable insight into the functional aspects of trait variation and evolution, it remains unclear how much QTV discovery can teach us about the wider principles of phenotypic evolution in natural populations. To the extent that phenotypic evolution occurs through complex polygenic changes with individually minor effects (Fisher 1918; Barton *et al.* 2017; Walsh and Lynch 2018), QTV discovery does not directly elucidate the broader patterns of polygenicity, epistasis, or gene-by-environment interactions. For one, QTV identification is labor-intensive; studies often identify multiple QTLs but map only 1 or 2 of the largest effects. For another, we are still best powered to uncover the largely additive variants of major effects (Rockman 2012).

For example, 2 classes of results have dominated the discovery list of QTV for life history traits. One is the laboratory-adapted alleles in the N2 background, as mentioned above and described in detail below. The other is variants that tend to be rare in the population and induce detrimental effects on life history (Evans

Box 3. The molecular basis of natural variation in *C. elegans* dauer formation

Wild *C. elegans* strains exhibit extensive variation in the propensity to form dauers in response to environmental factors (Viney *et al.* 2003; Diaz and Viney 2015; O'Donnell *et al.* 2018; Lee *et al.* 2019; Billard *et al.* 2020), and numerous studies have evaluated the genetic basis for this variation. Using recombinant inbred lines derived from crosses between the laboratory strain N2, which is responsive to environmental cues, and wild strain DR1350 or CB4856, which are less responsive, variation was mapped to 3, 24, or 36 genomic regions (Harvey *et al.* 2008; Green *et al.* 2013, 2014); fine-mapping on chromosome II identified 2 regions with opposing effects within CB4856 (O'Donnell *et al.* 2018). Some of the mapped regions were shared across studies (Green *et al.* 2014), but differences in experimental design, including the environmental context for dauer induction as well as strain identity, demonstrate substantial complexity in the genetic determinants of dauer plasticity.

In a genome-wide association analysis of 157 wild strains, Lee *et al.* (2019) mapped differences in response to a dauer pheromone component to 4 genomic regions, 1 of which was resolved to the molecular level: indel variants in 2 pheromone receptor genes, *srg-36* and *srg-37*. These deletion variants represent putative loss-of-function alleles and likely confer reduced pheromone sensitivity, yet occur naturally in 57 wild strains. As the *srg-37* deletion allele co-occurs with the alternate (nondeletion) allele in multiple populations, balancing selection may contribute to the maintenance of this polymorphism. Across the global strain collection, strains carrying the *srg-37* deletion allele were found to be more prevalent in human-associated, microbe-rich habitats such as rotting fruit or compost. Thus, the natural *srg-37* deletion may have emerged recently from ancestral populations and spread globally, driven by opportunities in emerging ecological niches by conferring a fitness advantage associated with (or in spite of) reduced pheromone sensitivity (Lee *et al.* 2019). Notably, deletion variants in *srg-36* and *srg-37* were also discovered to be favored during laboratory adaptation at high density (McGrath *et al.* 2011).

The mechanisms underlying natural variation in dauer induction go beyond differences in pheromone reception. The wild strain JU751 exhibits enhanced propensity to enter dauer, and QTL mapping using F2 recombinant inbred lines derived from a cross between JU751 and a wild isolate with typical dauer induction identified a 92-bp deletion in the presumptive promoter region of the gene *eak-3* (Billard *et al.* 2020). *eak-3* was previously discovered to modulate insulin-like signaling and affect dauer via the steroid hormone dafachronic acid, the central downstream component controlling the binary dauer decision (Zhang *et al.* 2008). The *eak-3* deletion causes constitutively reduced levels of dafachronic acid, thus lowering the environmental sensitivity threshold for dauer induction (Billard *et al.* 2020). Evolution of increased environmental sensitivity in the dauer decision by hormone level modulation is a surprising discovery, since constitutive hormonal changes should have pleiotropic effects (Gerisch *et al.* 2001; Schaedel *et al.* 2012; Antebi 2013). Indeed, the *eak-3* variant was found to delay postembryonic reproductive growth in favorable conditions, delaying the age at reproduction by several hours, and was rapidly outcompeted in environments promoting reproductive growth. Assuming the deletion provides a fitness advantage in stressful environments, this variant represents a trade-off between developmental timing and the environmental sensitivity of a plasticity switch (Billard *et al.* 2020) and reinforces the expectation that hormonal pleiotropy may engender trade-offs in life history (Finch and Rose 1995; Bourg *et al.* 2019).

et al. 2021). These also often turn out to be related to male function (Andersen and Rockman 2022). For example, males with a rare allele of the transcription factor *mab-23* cannot mate (Hodgkin and Doniach 1997; Lints and Emmons 2002), males carrying a retrotransposon-induced loss-of-function allele of *plg-1* do not deposit copulatory plugs on the hermaphrodite vulva after mating (Palopoli *et al.* 2008), males with a loss-of-function allele of *plep-1* deposit plugs on the excretory pores of other males (Noble *et al.* 2015). In these cases, the relaxed selection on male function likely failed to purge these deleterious, large-effect variants from the population.

Other examples may similarly represent relatively rare cases of variation, possibly arising from deleterious losses of function. Temperature-sensitive sterility in the BO strain is explained by mutations in *zyg-12* (Fatt and Dougherty 1963; Malone *et al.* 2003), and a rare deletion in *set-24* is largely responsible for the mortal germline phenotype, which also induces sterility over extended exposure to high temperature, in the strain MY10 (Frézal *et al.* 2018). Further, while sex determination is essentially invariant within *C. elegans*, mating system evolution into androdioecy by the female acquisition of sperm function likely occurred by few, but very dramatic, genetic changes (Ellis and Lin 2014; Haag *et al.* 2018; Cutter *et al.* 2019; Ellis 2022). These discoveries, though groundbreaking, may not capture the nature of the majority of heritable variation in life history in contemporaneous populations. In the next section, we describe evidence for significant complexity in the genetic basis for life history variation.

Polygenicity, hidden effects, and epistasis

Genetic architecture refers to structural aspects of the genetics of phenotypic variation, including the number of contributing variants (degree of polygenicity) and their effect sizes, frequency in the population, and dependencies on each other (epistasis) and on the environment (GxE). Life history components including fecundity, growth rate, body size, dauer formation, lifespan, reproductive timing, and male production have routinely been shown to have a polygenic basis (Gutteling, Doroszuk *et al.* 2007; Gutteling, Riksen *et al.* 2007; Rodriguez *et al.* 2012; Green *et al.* 2013, 2014; Andersen *et al.* 2014, 2015; Stastna *et al.* 2015; Zhu *et al.* 2015; Lim *et al.* 2021; Zhang *et al.* 2021), as expected for complex traits (Houle 1992; Mackay *et al.* 2009). Yet, mapping studies have also frequently detected large-effect regions that essentially behave in discrete, Mendelian-like fashion (Evans *et al.* 2021). Some of these are signals of valid large-effect QTV of evolutionary consequence, as described above. However, others may masquerade as individual contributions with large effect but mask hidden complexity.

For example, linkage mapping with RIAILs derived from N2 and CB4856 identified multiple large-effect loci associated with growth and reproduction, but NILs derived from the same strains varying over just a small interval on the X chromosome revealed effects similar in magnitude; if such effects were distributed over the whole genome, the RIAILs should have captured far greater phenotypic variance (Bernstein *et al.* 2019). These results are explained by the existence of numerous variants of opposing effect and lend strong support for the polygenic model of complex trait variation (Mackay *et al.* 2009; Boyle *et al.* 2017; Yengo *et al.* 2022), and in particular the pervasiveness of tightly linked antagonistic loci (Brown *et al.* 2016; Metzger and Wittkopp 2019; Schoech *et al.* 2020). These findings are a reminder to be mindful of making inferences about genetic architecture, given that many quantitative genetic approaches will be limited in their capacity to detect effects beyond those that are moderate-to-large and additive, i.e. expressed independently of other loci.

In fact, both molecular and evolutionary genetic research suggest that epistasis between alleles at different loci contributes significantly to variation in complex phenotypes like life history

Box 4. The molecular basis of reproductive life history variation via changes in egg-laying behavior

C. elegans egg laying can be inhibited by exposure to stressors, including starvation, hypoxia, thermal stress, osmotic stress, or pathogens (Schafer 2005). If stress exposure persists, it can trigger significant intrauterine retention of fertilized eggs, inducing larvae to hatch and undergo development within the mother. This phenomenon, known as matricidal hatching or facultative viviparity, ultimately leads to premature maternal death (Maupas 1900; Trent 1982; Chen and Caswell-Chen 2003, 2004). Despite this cost, the progeny may benefit from this behavioral change in food-scarce or stressful environments (Vigne *et al.* 2021; Mignerot *et al.* 2024).

Natural *C. elegans* strains exhibit considerable variation in the levels of egg retention and subsequent matricidal hatching in response to environmental factors (Vigne *et al.* 2021; Mignerot *et al.* 2024). In the most extreme case, strains retain eggs even under benign standard food conditions and therefore exhibit constitutive matricidal hatching. Mapping one of these variants, Vigne *et al.* (2021) identified the causative molecular change as a single-nucleotide mutation leading to an amino acid substitution in the calcium-activated potassium channel *kcnl-1* gene. This gain-of-function variant causes vulval muscle hyperpolarization that reduces egg-laying activity, leading to constitutively strong egg retention, internal hatching, and premature maternal death. Reversion to the canonical sequence of the KCNL-1 protein restores typical egg-laying, resulting in a 2-fold increase in lifetime offspring production.

Despite its deleterious fitness consequences, the *kncl-1* variant has been observed at low frequency across multiple populations and was isolated repeatedly across more than 15 years (Vigne *et al.* 2021; Mignerot *et al.* 2024). Competition experiments using reciprocal single-nucleotide allelic replacement lines showed that this variant can be maintained when the window of reproduction is restricted to early adult life or under conditions of fluctuating stress and nutrient availability, which may better resemble the ephemeral structure of the natural *C. elegans* habitat (Vigne *et al.* 2021). A more comprehensive examination of natural variation in egg retention, beyond the role of the *kcnl-1* variant, further demonstrated that increased egg retention in *C. elegans* is disadvantageous for mothers due to reduced survival and fertility but can confer benefits to their offspring.

Specifically, extended retention of eggs before laying leads to improved protection against environmental insults for the offspring and a competitive advantage arising from a significantly reduced extra-uterine egg-to-adult developmental time: longer-retained embryos hatch sooner, develop to reproductive maturity sooner, and outcompete shorter-retained embryos laid at the same time. Observed natural variation in *C. elegans* egg retention may, therefore, reflect a trade-off between fitness components expressed in mothers versus offspring (Mignerot *et al.* 2024).

traits (Cheverud and Routman 1995; Phillips 2008; Campbell *et al.* 2018), including in *C. elegans* (McGrath *et al.* 2009; Gaertner *et al.* 2012; Pollard and Rockman 2013; Glater *et al.* 2014; Large *et al.* 2017; Noble *et al.* 2017; Gao *et al.* 2018; Brady *et al.* 2019; Sterken *et al.* 2020; Fausett *et al.* 2023). This was clearly illustrated by the *C. elegans* multiparental experimental evolution (CeMEE) panel, in which inbred lines were derived from the hybridization of 16 wild parents followed by experimental evolution for up to 190 generations (Noble *et al.* 2017; Noble, Rockman et al. 2021). The phenotyping of several hundred CeMEE lines for 2 partly correlated life history traits, fertility, and adult body size, did not detect any additive QTL despite excellent mapping resolution to detect loci of small effect. Instead, ~40% of the variance in fertility was attributed to epistatic and strongly polygenic interactions. Notably, all pairwise interactions among loci exhibited sign epistasis, such that the phenotypic effects of a given QTL were reversed in the presence of another (Noble *et al.* 2017). The capacity of the CeMEE panel to detect such epistatic interactions, as well as additive small-effect loci, significantly advances our potential to resolve questions of genetic architecture and identify relevant variants in *C. elegans*. *Caenorhabditis* nematodes also hold significant promise for unraveling the nature of epistatic interactions between nuclear and mitochondrial components (Estes *et al.* 2023). Such mitonuclear interactions exhibit natural variation and contribute to variation in diverse life history phenotypes (Estes *et al.* 2011; Zhu *et al.* 2015, 2019; Bever *et al.* 2022).

Genotype-by-environment interactions

Life history traits vary by both genotype and environment; they also tend to exhibit substantial genetic variation in how they respond to the environment (Lynch and Walsh 1998). Significant GxE interactions are routinely observed for *C. elegans* life history traits (Braendle *et al.* 2008; Schulenburg and Félix 2017; Baugh and Hu 2020; Evans *et al.* 2021). For example, *C. elegans* strains cultured at varying temperatures show marked differences in thermal plasticity for fertility decay, fecundity, age at maturity, growth rate, and body size (Gutteling *et al.* 2007; Harvey and Viney 2007; Kammenga *et al.* 2007; Anderson, Albergotti *et al.* 2011; Petrella 2014; Poullet *et al.* 2015; Evans *et al.* 2017; Frézal *et al.* 2018; Maulana *et al.* 2022). Mapping the expression of growth and size phenotypes across a temperature gradient, a recent study demonstrated that some of the same loci that affect trait variation within environments may also affect plasticity across environments (Maulana *et al.* 2022). These observations of pervasive GxE reinforce our understanding of life history traits as highly complex and context dependent, and the importance of including environmental context in both experimental design and inferences about fitness.

Trait correlations

Phenotypic correlation occurs when traits covary among individuals, and traits exhibit genotypic correlation if the relationship is heritable. The presence of genotypic correlations between traits indicates that they cannot evolve independently, and negative correlations are of particular interest because they may indicate trade-offs (Cheverud 1988; Falconer and Mackay 1996). Identifying trait correlations and elucidating their genetic basis is consequently a central aim of life history research (Houle 1991; Roff 1992; Stearns 1992; Roff and Fairbairn 2007; Chebib and Guillaume 2017). Specifically, we would like to know the extent to which trait correlations manifest by pleiotropic effects of individual loci vs linkage between loci that act separably on 2 or more traits. Although this problem has long been recognized, our understanding of the mechanistic basis of life history trade-offs in experimental and natural populations is still surprisingly limited (Riska 1989; Houle 1991; Ketterson and Nolan 1992; Anderson, Reynolds *et al.* 2011; Flatt and Heyland 2011; Hughes and Leips 2016; Billard *et al.* 2020). However, *C. elegans* MA experiments indicate that most deleterious new mutations act pleiotropically, affecting virtually all fitness components and leading to positive mutational correlations (Vassilieva and Lynch 1999; Knight *et al.* 2001; Azevedo *et al.* 2002; Baer *et al.* 2005; Estes *et al.* 2005; Ostrow *et al.* 2007).

Insights from experimental evolution

Experimental evolution involves observing the real-time evolution of traits under defined conditions (Garland and Rose 2009). For life history research, it has played a central role in elucidating

the genetic basis of trait variation and correlations among fitness components, and over the past 2 decades, *C. elegans* has become established as an experimental evolution model and generated unique insights into the dynamics governing life history adaptation (Gray and Cutter 2014; Teotónio *et al.* 2017). Leveraging the ease by which the *C. elegans* sex ratio and mating system can be genetically altered, experimentalists have examined the selective forces shaping transitions between outcrossing and selfing to show that adaptation (in genetically diverse populations) generally occurs through standing genetic variation rather than novel mutations, and that high levels of outcrossing can be maintained over time in diverse environmental regimes (Morran *et al.* 2009; Anderson *et al.* 2010; Teotonio *et al.* 2012; Masri *et al.* 2013; Guzella *et al.* 2018). A caveat to all experimental evolution, however, is whether the findings are straightforwardly relevant to natural populations. For example, particular ecological conditions may favor the evolutionary transition from outcrossing to selfing through selection for reproductive assurance (Theologidis *et al.* 2014), i.e. the capacity for autonomous reproduction that ensures persistence in environments where potential mates are scarce (Stebbins 1957).

Artificial selection, in which the experimenter (rather than the experimental environment) selects individuals with specific phenotypic values, has also been pivotal in life history research (Garland and Rose 2009), specifically with regard to observing correlated responses to selection to elucidate life history trade-offs. This approach has only rarely been employed in *C. elegans* (Azevedo *et al.* 2002), in contrast to the rich artificial selection literature in *Drosophila* (Prasad and Joshi 2003; Flatt 2020).

C. elegans has, however, been used extensively in MA studies, a mode of experimental evolution that captures the fitness consequences of spontaneous mutations (Teotónio *et al.* 2017). MA experiments minimize selection by isolating and maintaining replicate MA lines, which are subjected to repeated severe bottlenecks across many generations. This arduous task is facilitated in *C. elegans* as a single hermaphrodite larva can be transferred from 1 generation to the next. MA experiments in *C. elegans* have yielded insight into the mutational decay of fitness and the mutational variances and covariances for life history traits such as self-fertility, developmental time, age at maturity, competitive fitness, and body size (Keightley and Caballero 1997; Vassilieva and Lynch 1999; Denver *et al.* 2000; Peters and Keightley 2000; Peters *et al.* 2003; Baer *et al.* 2005; Estes *et al.* 2005; Baer 2008; Salomon *et al.* 2009). While mutational responses differ across traits, genotypes, and species, life history traits decay rapidly in the absence of selection; as expected, they decay more rapidly than other traits. In *C. elegans*, overall fitness is estimated to decrease at a rate of ~0.1% per generation (Keightley and Caballero 1997; Vassilieva and Lynch 1999; Baer *et al.* 2005). The rate and distribution of mutational effects on fitness thus also provide insights into the genetic trait architecture underlying life history phenotypes (Eyre-Walker 2010; Gilbert *et al.* 2022).

Life history evolution via inadvertent laboratory adaptation

While the reference strain N2 is by far the predominant subject in *C. elegans* laboratories, its biology is unique and atypical within the species, strongly shaped by the process of laboratory adaptation (Sterken *et al.* 2015). While perhaps disquieting to some in the community, this discovery has generated valuable insights into the domestication syndrome, in particular how molecular changes have modulated behavior and life history traits to increase fitness in the specific environment of the laboratory (McGrath *et al.* 2009, 2011; Weber *et al.* 2010; Duveau and Félix 2012; Andersen *et al.* 2014; Sterken *et al.* 2015; Large *et al.* 2016, 2017; Crombie *et al.* 2022). Most notably, the well-characterized N2 allele of the neuropeptide receptor gene *npr-1* causes unique behavioral phenotypes and a distinct life history by affecting developmental time, age at maturity, and fecundity (Gloria-Soria and Azevedo 2008; Weber *et al.* 2010; Andersen *et al.* 2014). The effects of the N2 *npr-1* allele and another N2-specific allele, in the gene *glb-5*, are highly pleiotropic and cause changes in behavior and energy homeostasis that are ultimately responsible for the enhanced fitness of N2 in laboratory conditions (Zhao *et al.* 2018).

The strain LSJ2, originally derived from N2 and maintained in high-density axenic liquid culture for a period of 50 years, likewise exhibits strong life history adaptation to its artificial environment (McGrath *et al.* 2011; Large *et al.* 2016, 2017; Xu *et al.* 2019; Zhao *et al.* 2020). LSJ2 has a strongly reduced sensitivity to dauer-inducing pheromone, the main environmental cue inducing dauer formation at high population density; in the liquid environment, high pheromone concentration was no longer predictive of food exhaustion and entering the dauer stage would thus have been detrimental. The insensitivity in LSJ2 arises from the loss of 2 chemoreceptor genes, the G-protein coupled receptors *srg-36* and *srg-37* (McGrath *et al.* 2011). In a fascinating instance of parallel evolution, deletions in the 2 *srg* genes were also found to have occurred in multiple independently derived lines under adaptation to liquid culture, not only in *C. elegans* but in the distantly related *C. briggsae* as well (McGrath *et al.* 2011). Even more remarkable is the fact that deletions affecting the same chemoreceptor genes also modulate variation in sensitivity to pheromone in natural *C. elegans* populations (Lee *et al.* 2019), as mentioned above (Box 3).

Reminiscent of the large effect of the N2 *npr-1* allele, LSJ2 exhibits additional differences from N2, ranging from sperm size to reproductive timing, most of which were mapped to mutations in the chromatin remodeling factor *nurf-1* (Large *et al.* 2016, 2017; Gimond *et al.* 2019; Xu *et al.* 2019). The *nurf-1* variant provides a fitness advantage in the novel liquid environment compared to the ancestral laboratory conditions of solid medium (Large *et al.* 2016, 2017). Notably, this major-effect variant explained antagonistically pleiotropic effects on life history by decreasing early life reproductive effort but increasing late-life reproduction and extending lifespan (Large *et al.* 2016, 2017). The discovery of these loci provides insights into the changes underlying adaptation to "unnatural" laboratory conditions, with large, pleiotropic effects on life history traits, as typically observed during laboratory adaptation and domestication across diverse taxa (Doebley *et al.* 2006; Driscoll *et al.* 2009; De Chiara *et al.* 2022). Their molecular genetic analysis in *C. elegans*, however, offers some of the most detailed insights into the mechanistic basis of metazoan life history evolution.

Life history evolution beyond *C. elegans*

A primary focus of life history research lies in unraveling the evolution of alternative life histories among different species and major life history transitions across evolutionarily distant taxa (Harvey and Pagel 1998; Flatt and Heyland 2011). Such comparative life history analyses aim to characterize phylogenetic patterns—and constraints—governing life history diversity and discern the ecological factors that favor the adoption of specific life history strategies. *C. elegans* has emerged as a useful reference species for comparative analysis of nematode genomes, developmental processes, and life histories, such as variation in

reproductive mode. *C. elegans* can now be placed into a well-resolved phylogenetic context within the genus *Caenorhabditis* (Kiontke, Félix *et al.* 2011; Stevens *et al.* 2019), representing a valuable comparative framework to interpret and better understand *C. elegans* biology, in particular, life history transitions, such as the evolution of androdioecy from a dioecious ancestor. The species-rich phylum of nematodes further provides an outstanding resource to explore the evolution of highly diversified life histories in thousands of species spanning various ecological niches.

Evolution of mating systems and sex ratios in the genus *Caenorhabditis*

The genus *Caenorhabditis* now comprises over 70 culturable species, many of which have been whole-genome sequenced (Kiontke, Félix *et al.* 2011; Félix *et al.* 2014; Stevens *et al.* 2019, 2020; Dayi *et al.* 2021; Sloat *et al.* 2022). Phylogenetic studies, supported by comparative molecular analysis of germ line sex determination, show that androdioecy has been independently derived in 3 instances (*C. briggsae*, *C. elegans*, and *C. tropicalis*) from the predominant, ancestral dioecious (male–female) reproductive mode (Guo *et al.* 2009; Kiontke, Félix *et al.* 2011; Thomas *et al.* 2012). How *Caenorhabditis* androdioecy evolved from a dioecious ancestor through modification of sex determination pathways, genetically well-characterized in *C. elegans*, has been at the center of nematode evo-devo research (Haag *et al.* 2018). Overall, the repeated evolution of androdioecy in *Caenorhabditis* seems to have been facilitated by the mode of XX/XO sex determination, i.e. the lack of sex chromosomes. Moreover, hermaphrodites possess a female soma, with the male function of hermaphrodites being essentially limited to the production of sperm cells in an otherwise female context (Thomas *et al.* 2012; Ellis and Lin 2014; Ellis 2022). Molecular genetic studies support this view as one or few mutations can be sufficient to transform *C. elegans* hermaphrodites into spermless females (Schedl and Kimble 1988; Guo *et al.* 2009) or *C. remanei* females into self-fertilizing hermaphrodites (Baldi *et al.* 2009). For comprehensive discussion on the evolution of androdioecy and its consequences in *Caenorhabditis*, see Ellis and Lin (2014), Haag *et al.* (2018); Cutter *et al.* (2019), and Ellis (2022).

Beyond aiming to understand the evolutionary transitions to androdioecy and its extensive ramifications on all aspects of biology, comparative studies involving various *Caenorhabditis* nematodes have been employed to address questions related to sexual selection, including sexual conflict and sex ratio evolution (Cutter *et al.* 2019). Sex ratio theory is a prominent aspect of life history theory, and central to evolutionary biology. Although theory predicts equal 1:1: male–female sex ratios in diploid species to predominate, many exceptions occur and a key aim is to understand which ecological factors drive such sex ratio bias (Fisher 1930; Hamilton 1967; Charnov 1982). Recent work suggests that outcrossing *Caenorhabditis* species offers a promising system to study the evolution of sex ratio bias (Huang *et al.* 2023; Sloat and Rockman 2023). *Caenorhabditis* species exhibit substantial inter- and intraspecific variation in sex ratios, with an overall tendency for female/hermaphrodite-biased sex ratios (Huang *et al.* 2023). Mechanistically, this female bias can be, at least partly, explained by competition between sperm, with increased competitivity of the X-bearing sperm vs sperm lacking the X chromosome; however, other mechanisms are likely involved (Van Goor *et al.* 2021; Huang *et al.* 2023; Sloat and Rockman 2023). Female-biased sex ratios are expected under local mate competition, that is, in strongly subdivided populations where natural selection favors the biased production of the less competitive sex to reduce direct competition for mates (Hamilton 1967). The observation of female-biased sex ratios thus aligns with the colonization patterns of most *Caenorhabditis* species, thriving in highly ephemeral and patchily distributed substrates (Petersen *et al.* 2015; Ferrari *et al.* 2017; Richaud *et al.* 2018; Sloat *et al.* 2022). The *Caenorhabditis* genus thus offers an ideal system for further studies aiming to integrate the study of evolution, ecology, and genetics of sex ratio bias.

Generalist vs specialist *Caenorhabditis* life histories

The life history framework aims to understand why and how different species have evolved alternative strategies for survival, reproduction, and resource utilization. A fundamental distinction lies in the contrast between generalist and specialist species, where life history strategies diverge based on the degree of ecological specialization (Futuyma and Moreno 1988). Although, at least superficially, many *Caenorhabditis* species resemble each other morphologically (cryptic species), they harbor ample variation in diverse phenotypes, including reproductive mode and diverse life history traits (Haag *et al.* 2007; Sudhaus and Kiontke 2007; Kiontke, Félix *et al.* 2011; Félix *et al.* 2014; Stevens *et al.* 2019). What remains more enigmatic is how interspecific variation in particular life history attributes connects with species-specific ecologies. *Caenorhabditis* nematodes have been found across the globe in diverse habitats and substrates, mostly on decaying microbe-rich plant matter, such as rotting fruit and flowers, and invertebrates associated with these substrates (Kiontke, Félix *et al.* 2011; Stevens *et al.* 2019). Most *Caenorhabditis* species are presumed to display dispersal during the dauer stage via invertebrate hosts (phoresy), including insects, millipedes, isopods, and gastropods, to colonize novel substrates (Kiontke 2006; Stevens *et al.* 2019). A number of species have been isolated from specific (e.g. figs) or distinct substrates (e.g. vertebrates, soil, mushrooms), sometimes in close association with particular insect hosts or carriers (Sudhaus 1976; Kiontke 1997, 2006; Kiontke, Félix *et al.* 2011; Frezal and Félix 2015; Kanzaki *et al.* 2018; Stevens *et al.* 2019; Dayi *et al.* 2021; Sun *et al.* 2022). Although our understanding of the natural history and ecology of most species remains extremely limited, these observations imply that *Caenorhabditis* species can be discerned based on apparent generalist and specialist life histories, which are likely to have significant repercussions on demography, and hence, genetic diversity (Kiontke 2006; Li *et al.* 2014).

Recurrent isolation of the same species across diverse habitats and substrates, or across a large spectrum of invertebrate carriers, suggests that they are generalists. Such generalists include the 3 androdioecious species, with *C. briggsae* being the most common species across the globe, and *C. elegans* and *C. tropicalis*, which are the most frequently isolated species in temperate and tropical regions, respectively (Kiontke, Félix *et al.* 2011; Félix *et al.* 2014; Ferrari *et al.* 2017). Several common outcrossing species, in particular *C. remanei* (temperate) and *C. brenneri* (tropical), are apparent generalists as they occupy diverse, often human-associated, ecological niches, like the 3 androdioecious *Caenorhabditis* species. On the other hand, a handful of species (*C. astrocarya*, *C. auriculariae*, *C. bovis*, *C. drosophilae*, *C. inopinata*, *C. japonica*, *C. niphades*) exhibit specialist life styles as they display strong specificity in substrate and/or associated invertebrate dispersal hosts (Kiontke 1997, 2006; Kiontke, Félix *et al.* 2011; Kiontke, Hironaka *et al.* 2011; Ferrari *et al.* 2017; Kanzaki *et al.* 2018; Stevens *et al.* 2019, 2020; Dayi *et al.* 2021; Sun *et al.* 2022). The most exotic ecological niche has been observed for *C. bovis*, which thrives in the

ears of cattle at temperatures of 37°C, likely by engaging in phoretic associations with flies, and leading to pathogenic symptoms in the host (Kreis 1964; Stevens *et al.* 2020). Together with genomic evidence, this suggests that *C. bovis* has evolved toward a parasitic life style, derived from a free-living ancestral state (Stevens *et al.* 2020). Quite unexpectedly, the recently discovered *C. inopinata*, and sister species of *C. elegans*, inhabits a highly specialized niche and display a unique morphology, distinct from virtually all other *Caenorhabditis*: *C. inopinata* lives enclosed in fresh figs of *Ficus septica* and (dauer) dispersal between fruits seems to be exclusively ensured by taxon-specific pollinating wasps (Kanzaki *et al.* 2018; Woodruff and Phillips 2018). The currently best-understood example of a specialist *Caenorhabditis* life history occurs in the male–female species *C. japonica*, which lives in a close phoretic relationship with a single hemipteran insect species (Tanaka *et al.* 2010; Kiontke, Félix *et al.* 2011; Okumura *et al.* 2013; Yoshiga *et al.* 2013; Li *et al.* 2014). The life cycle of the gonochoristic *C. japonica* is tightly connected to the life cycle of its insect host, which itself is a specialist species, whose life cycle is synchronized with the exploitation of a seasonal 2-month period of fruit production of the tree *Schoepfia jasminodora* (Yoshiga *et al.* 2013). Reproductive growth and dispersal in both insect and nematode exclusively take place during this short time window. For the rest of the year, both species remain in a quiescent state, with *C. japonica* existing in the form of dauers that colonize the insect host (Yoshiga *et al.* 2013). The specialized phoresy of *C. japonica*, together with strong fluctuations in resource and host availability, and severe population bottlenecks, seems to be likely causal explanations for the low intraspecific nucleotide diversity observed for this species, compared to other (generalist) outcrossing *Caenorhabditis* species (Li *et al.* 2014). These findings suggest an underappreciated link between life history, genetic diversity, and ecological niche in *Caenorhabditis* nematodes.

Life history diversity across the phylum Nematoda

The remarkable diversification of nematode life cycles provides a rich resource for exploring the macroevolution of life history strategies, underlying phylogenetic patterns and trends, and their ecological context and genomic correlates. The phylum Nematoda currently includes ~30,000 described species, with the possibility of an additional million species yet to be discovered (Lee 2002; Lambshead 2004; Porazinska *et al.* 2009; Hodda 2022). Nematodes have colonized virtually all ecological niches and exhibit a remarkable divergence in morphology and lifestyles, encompassing free-living modes, as well as facultative or obligate plant and animal parasitic life cycles involving associations with 1 or more invertebrate or vertebrate host organisms (Blaxter *et al.* 1998; De Ley and Blaxter 2004; Blaxter and Koutsovoulos 2014; Ahmed and Holovachov 2021). A widely accepted phylogenetic framework defines 3 major branches (Enoplia, Dorylaimia, and Chromadoria) subdivided into 5 clades (Blaxter *et al.* 1998; De Ley and Blaxter 2004; Blaxter and Koutsovoulos 2014). *C. elegans* groups within the suborder Rhabditina (clade V), which comprises an incredible diversity of free-living and parasitic species, including many entomopathogenic species as well as biomedically important mammalian parasites with highly specialized, complex life cycles (Kiontke and Fitch 2005; Ley 2006; Blaxter and Koutsovoulos 2014).

As has long been appreciated (Maupas 1900; Nigon and Félix 2017), nematodes display great diversity in reproductive systems, ranging from the predominant mode of dioecy, with highly variable sex ratios, to derived modes, such as androdioecy, parthenogenesis, or pseudogamy (sperm-activated parthenogenesis) (Pires-daSilva 2007; Denver *et al.* 2011; Van Goor *et al.* 2021). Within a single genus, such as *Panagrolaimus*, divergent reproductive strategies exist, encompassing sexual, hermaphroditic, and parthenogenetic species (Lewis *et al.* 2009). Even the same species can exhibit mixed mating systems, such as trioecy with the coexistence of females, males, and hermaphrodites, e.g. in *Auanema* (Félix 2004; Kanzaki *et al.* 2017), or alternation between reproductive modes (heterogony), e.g. between dioecy and hermaphroditism or parthenogenesis, whose expression coincides with the free-living and parasitic phases of the life cycle, for example, in the animal-parasitic genus *Strongyloides* (Pires-daSilva 2007; Streit 2008; Denver *et al.* 2011). Life cycle switches between reproductive modes, and between free-living vs parasitic stages, in these and other species are generally plastic, dependent on maternal phenotype and other factors, such as density or temperature (Pires-daSilva 2007; Streit 2008; Denver *et al.* 2011; Sommer and Ogawa 2011). Thus, there is not only an extreme diversity of nematode lifestyles across thousands of species, but a single genotype may express multiple alternative life cycle stages with contrasting, often specialized life histories, underlining the central importance of plasticity in nematode life history regulation.

Parasitism of animals and plants has arisen at least 15 times independently in nematodes (Blaxter and Koutsovoulos 2014). By integrating insights from natural history, systematics, and *C. elegans* molecular genetics, one of the best-understood life cycle transitions in nematodes is the shift from free-living to parasitic lifestyles in Rhabditina nematodes. At least 3 lineages within this group have independently evolved zooparasitism from free-living ancestors, specifically through modification of the dauer larval stage into an infective juvenile stage observed in parasitic species (Ley 2006; Crook 2014; Vlaar *et al.* 2021). The dauer stage, the stress-resistant and phoretically dispersing stage in free-living species, occurs during the third larval stage, which aligns with the parasitic life cycle phase, referred to as the infective stage (iL3). Hence, the various behavioral and physiological characteristics of the dauer stage can be considered preadaptations that have facilitated nematode parasitism in many species across the Rhabditina (Osche 1956; Sudhaus 2010; Blaxter and Koutsovoulos 2014). Like dauer larvae, iL3s undergo developmental arrest, display similar morphological characteristics, and exhibit increased stress resistance. The control of iL3 entry is governed by environmental stimuli like those regulating dauer induction, such as temperature or volatile pheromone compounds. Comparative phylogenetic and molecular genetic approaches further show that the formation of dauer and infective stages may involve similar functional architectures, such as neuroendocrine processes via homologous neurons, involving IIS and steroid hormone signaling, i.e. DA DAF-12 signaling (Ashton *et al.* 1998; Hallem *et al.* 2007; Ogawa *et al.* 2009; Wang *et al.* 2009). Although certain central molecular signaling events during *C. elegans* induction, e.g. TGF-β signaling, appear to have divergent functions during iL3 formation in parasites, genetic research on the iL3 stage in various nematode taxa globally supports the common origin of dauer and infective larvae (Crook 2014; Gilabert *et al.* 2016; Vlaar *et al.* 2021).

Although much progress has been made in deciphering the genomic correlates of lifestyle diversification across nematodes, our understanding of evolutionary ecological forces driving transitions between different lifestyles and reproductive modes is relatively restricted, mainly due to limited opportunities for testing hypotheses about character evolution within well-resolved phylogenies. However, together with molecular phylogenetic investigation of diverse nematode groups, *C. elegans* biology, has provided an entry point for in-depth comparative analyses of

life history evolution at molecular and cellular levels. In addition to the *Caenorhabditis* genus, several cultivable nematode genera or species have been established as invaluable model systems for studying diverse life history phenomena, such as reproductive system evolution and life history plasticity, e.g. in *Pristionchus* (Sommer 2015), *Auanema* (Tandonnet *et al.* 2018), *Tokorhabditis* (Yamashita *et al.* 2023), *Mesorhabditis* (Launay *et al.* 2020), or *Panagrolaimus* (Schiffer *et al.* 2019). Establishment of several parasitic species for genetic research has advanced our understanding of remarkably specialized and complex life cycles associated with host specialization, including mammalian parasites (e.g. *Strongyloides*, *Brugia*, *Ascaridia*, *Haemonchus*), insect parasites (*Heterorhabditis*, *Steinernema*), and plant parasitic nematodes, such as root-knot nematodes of the genus *Meloidogyne* (Castagnone-Sereno *et al.* 2013; Blaxter and Koutsovoulos 2014; Zamanian and Andersen 2016; Vadnal *et al.* 2017; Liu *et al.* 2020; Cao 2023; Collins and Andersen 2023; Al-Jawabreh *et al.* 2024). The in-depth exploration of *C. elegans* biology for half a century has been instrumental for conducting comparative analyses of the vast, fascinating diversity of nematode lifestyles. Yet, this research endeavor also serves as a stark reminder that concentrating exclusively on a single model species can only capture 1 idiosyncratic life history amid countless divergent, often eccentric, possibilities.

Conclusions and perspectives

C. elegans has proven to be a powerful, integrative organismal system to investigate the genetics and evolution of life history traits as well as broader questions within the life history framework. A major contribution of *C. elegans* to the life history framework has been to elucidate how various signaling pathways coordinate processes to determine major life history decisions and trade-offs, e.g. developmental timing, dauer formation, and reproductive plasticity, often regulated by endocrine processes involving the same hormones (Fielenbach and Antebi 2008; Antebi 2013). One promising avenue for future research involves examining how developmental processes mediated at the molecular level integrate to generate higher-level phenotypes, including life history traits. The framework of phenotypic integration may offer an inroad to explicitly test this question. A number of studies have begun addressing aspects of phenotypic integration, particularly in relation to allometry and scaling in *C. elegans* (Patel *et al.* 2002; Farhadifar *et al.* 2015; Uppaluri *et al.* 2016; Stojanovski *et al.* 2023). Extending these investigations to analyze life history trait variation across micro- and macroevolutionary scales, as well as experimental evolution, presents a promising approach.

A motivating question has been to resolve whether specific genes with roles in fundamental life history processes discovered via molecular genetics harbor natural genetic variation and contribute to the observed phenotypic variation in wild populations (Braendle *et al.* 2011). While pursued in *D. melanogaster* (Paaby and Schmidt 2008; Paaby *et al.* 2010), a "candidate gene" approach to assessing functional genetic variation in life history traits has been largely absent from *C. elegans* research, perhaps for several reasons. One, by the time wild isolate collections were well established in the *C. elegans* community, whole-genome genotyping methods were already enabling mapping as a method to evaluate natural variation (Cook *et al.* 2017). Two, the demographic features of *D. melanogaster* that induce molecular signatures of adaptation like clinal allele frequencies, including high rates of recombination and gene flow (David and Capy 1988; Paaby and Schmidt 2009; Adrion *et al.* 2015), are not present in *C. elegans* (Thomas *et al.* 2015; Lee *et al.* 2021; Andersen and Rockman 2022). Nevertheless, such an investigation might contribute complementary insight into functional variation identified through mapping approaches (Evans *et al.* 2021).

The ongoing development of systems genetics and quantitative genetics for deciphering natural trait variation holds the potential to advance our understanding of complex trait genetic architecture and evolution. This involves dissecting underlying polygenic factors, epistatic interactions, and GxE. By pushing the frontier of these methods in multicellular systems, *C. elegans* research contributes to a deeper understanding of the general principles governing complex trait variation and evolution. Although the conundrum of how to effectively merge molecular and statistical genetics persists, an integration of these approaches represents a crucial step forward (Rockman 2012; Travisano and Shaw 2012; Lee *et al.* 2014; Boyle *et al.* 2017; Barghi *et al.* 2020; Bergelson *et al.* 2021; Fagny and Austerlitz 2021; Whiteman 2022), and which *C. elegans* is uniquely positioned to leverage, perhaps better than any other metazoan model organism.

Finally, to better understand *C. elegans* life history itself, we need innovative approaches to capture its ecology and fitness-determining factors, including generation time, offspring numbers across seasons, dauer induction frequency, effective population sizes, dispersal and colonization rates, metapopulation dynamics, and the roles of males and outcrossing. Additionally, key ecological determinants such as microbial interactions, phoretic associations, niche specialization, and species assemblies must be considered. Integrating these ecological studies with research on natural genotypic and phenotypic variation will provide deeper insights into the evolutionary history and genetic diversification of *C. elegans* across various ecological niches. Significant efforts have already been devoted to advancing the understanding of natural variation in *Caenorhabditis* nematodes, facilitated by novel resources, including CaeNDr (Crombie *et al.* 2024), CeMEE (Noble *et al.* 2017), and CeMbio (Dirksen *et al.* 2020), gaining widespread adoption within the *C. elegans* community.

Acknowledgments

We would like to thank R. Baugh, A. Cutter, M. A. Félix, H. Teotónio, and the reviewers for helpful comments and advice.

Funding

This work has been supported by the Agence Nationale de la Recherche (ANR), the Centre National de la Recherche Scientifique (CNRS), the Institut national de la santé et de la recherche médicale (Inserm), and the Université Côte d'Azur to C.B.; and by the National Science Foundation (United States) and Simons Foundation via the Southeast Center for Mathematics and Biology (NSF 1764406), NSF IOS-2319796, and the Georgia Institute of Technology to A.P.

Conflicts of interest

The author(s) declare no conflict of interest.

Literature cited

Acasuso-Rivero C, Murren CJ, Schlichting CD, Steiner UK. 2019. Adaptive phenotypic plasticity for life-history and less fitness-

related traits. Proc Biol Sci. 286(1904):20190653. doi:10.1098/rspb.2019.0653.
Adrion JR, Hahn MW, Cooper BS. 2015. Revisiting classic clines in *Drosophila melanogaster* in the age of genomics. Trends Genet. 31(8):434–444. doi:10.1016/j.tig.2015.05.006.
Ahmed M, Holovachov O. 2021. Twenty years after De Ley and Blaxter-how far did we progress in understanding the phylogeny of the phylum Nematoda? Animals (Basel). 11(12):3479. doi:10.3390/ani11123479.
Al-Jawabreh R, Anderson R, Atkinson LE, Bickford-Smith J, Bradbury RS, Breloer M, Bryant AS, Buonfrate D, Cadd LC, Crooks B, *et al.* 2024. *Strongyloides* questions—a research agenda for the future. Philos Trans R Soc Lond B Biol Sci. 379(1894):20230004. doi:10.1098/rstb.2023.0004.
Andersen EC, Bloom JS, Gerke JP, Kruglyak L. 2014. A variant in the neuropeptide receptor npr-1 is a major determinant of *Caenorhabditis elegans* growth and physiology. PLoS Genet. 10(2):e1004156. doi:10.1371/journal.pgen.1004156.
Andersen EC, Gerke JP, Shapiro JA, Crissman JR, Ghosh R, Bloom JS, Félix M-A, Kruglyak L. 2012. Chromosome-scale selective sweeps shape *Caenorhabditis elegans* genomic diversity. Nat Genet. 44(3):285–290. doi:10.1038/ng.1050.
Andersen EC, Rockman MV. 2022. Natural genetic variation as a tool for discovery in *Caenorhabditis* nematodes. Genetics. 220(1):iyab156. doi:10.1093/genetics/iyab156.
Andersen EC, Shimko TC, Crissman JR, Ghosh R, Bloom JS, Seidel HS, Gerke JP, Kruglyak L. 2015. A powerful new quantitative genetics platform, combining *Caenorhabditis elegans* high-throughput fitness assays with a large collection of recombinant strains. G3 (Bethesda). 5(5):911–920. doi:10.1534/g3.115.017178.
Anderson JL, Albergotti L, Ellebracht B, Huey RB, Phillips PC. 2011. Does thermoregulatory behavior maximize reproductive fitness of natural isolates of *Caenorhabditis elegans*? BMC Evol Biol. 11:157. doi:10.1186/1471-2148-11-157.
Anderson JL, Morran LT, Phillips PC. 2010. Outcrossing and the maintenance of males within *C. elegans* populations. J Hered. 101(Suppl 1):S62–S74. doi:10.1093/jhered/esq003.
Anderson JL, Reynolds RM, Morran LT, Tolman-Thompson J, Phillips PC. 2011. Experimental evolution reveals antagonistic pleiotropy in reproductive timing but not life span in *Caenorhabditis elegans*. J Gerontol A Biol Sci Med Sci. 66(12):1300–1308. doi:10.1093/gerona/glr143.
Angeles-Albores D, Aprison EZ, Dzitoyeva S, Ruvinsky I. 2023. A *C. elegans* male pheromone feminizes germline gene expression in hermaphrodites and imposes life-history costs. Mol Biol Evol. 40(6):msad119. doi:10.1093/molbev/msad119.
Angelo G, Van Gilst MR. 2009. Starvation protects germline stem cells and extends reproductive longevity in *C. elegans*. Science. 326(5955):954–958. doi:10.1126/science.1178343.
Antebi A. 2013. Steroid regulation of *C. elegans* diapause, developmental timing, and longevity. Curr Top Dev Biol. 105:181–212. doi:10.1016/B978-0-12-396968-2.00007-5.
Apfeld J, Kenyon C. 1999. Regulation of lifespan by sensory perception in *Caenorhabditis elegans*. Nature. 402(6763):804–809. doi:10.1038/45544.
Aprison EZ, Dzitoyeva S, Angeles-Albores D, Ruvinsky I. 2022. A male pheromone that improves the quality of the oogenic germline. Proc Natl Acad Sci U S A. 119(21):e2015576119. doi:10.1073/pnas.2015576119.
Aprison EZ, Dzitoyeva S, Ruvinsky I. 2022. The serotonin circuit that coordinates germline proliferation and egg laying with other reproductive functions in *Caenorhabditis elegans*. Proc Biol Sci. 289(1987):20220913. doi:10.1098/rspb.2022.0913.
Ashe A, Bélicard T, Le Pen J, Sarkies P, Frézal L, Lehrbach NJ, Félix M-A, Miska EA. 2013. A deletion polymorphism in the *Caenorhabditis elegans* RIG-I homolog disables viral RNA dicing and antiviral immunity. eLife. 2:e00994. doi:10.7554/eLife.00994.
Ashton FT, Bhopale VM, Holt D, Smith G, Schad GA. 1998. Developmental switching in the parasitic nematode *Strongyloides stercoralis* is controlled by the ASF and ASI amphidial neurons. J Parasitol. 84(4):691–695. doi:10.2307/3284571.
Austad SN, Hoffman JM. 2018. Is antagonistic pleiotropy ubiquitous in aging biology? Evol Med Public Health. 2018(1):287–294. doi:10.1093/emph/eoy033.
Azevedo RBR, Keightley PD, Laurén-Määttä C, Vassilieva LL, Lynch M, Leroi AM. 2002. Spontaneous mutational variation for body size in *Caenorhabditis elegans*. Genetics. 162(2):755–765. doi:10.1093/genetics/162.2.755.
Azorsa DO, Arora S. 2018. High-Throughput RNAi Screening: Methods and Protocols. New York (NY): Springer.
Baer CF. 2008. Quantifying the decanalizing effects of spontaneous mutations in rhabditid nematodes. Am Nat. 172(2):272–281. doi:10.1086/589455.
Baer CF, Shaw F, Steding C, Baumgartner M, Hawkins A, Houppert A, Mason N, Reed M, Simonelic K, Woodard W, *et al.* 2005. Comparative evolutionary genetics of spontaneous mutations affecting fitness in rhabditid nematodes. Proc Natl Acad Sci U S A. 102(16):5785–5790. doi:10.1073/pnas.0406056102.
Baldi C, Cho S, Ellis RE. 2009. Mutations in two independent pathways are sufficient to create hermaphroditic nematodes. Science. 326(5955):1002–1005. doi:10.1126/science.1176013.
Barghi N, Hermisson J, Schlötterer C. 2020. Polygenic adaptation: a unifying framework to understand positive selection. Nat Rev Genet. 21(12):769–781. doi:10.1038/s41576-020-0250-z.
Bargmann CI. 2006. Chemosensation in *C. elegans*. Wormbook. 1–29. doi:10.1895/wormbook.1.123.1.
Barker DM. 1992. Evolution of sperm shortage in a selfing hermaphrodite. Evolution. 46(6):1951. doi:10.2307/2410043.
Barnes AI, Partridge L. 2003. Costing reproduction. Anim Behav. 66(2):199–204. doi:10.1006/anbe.2003.2122.
Barrière A, Félix M-A. 2005a. High local genetic diversity and low outcrossing rate in *Caenorhabditis elegans* natural populations. Curr Biol. 15(13):1176–1184. doi:10.1016/j.cub.2005.06.022.
Barrière A, Fèlix M-A. 2005b. Natural variation and population genetics of *Caenorhabditis elegans*. WormBook. 1–19. doi:10.1895/wormbook.1.43.1.
Barrière A, Félix M-A. 2007. Temporal dynamics and linkage disequilibrium in natural *Caenorhabditis elegans* populations. Genetics. 176(2):999–1011. doi:10.1534/genetics.106.067223.
Barrière A, Yang S-P, Pekarek E, Thomas CG, Haag ES, Ruvinsky I. 2009. Detecting heterozygosity in shotgun genome assemblies: lessons from obligately outcrossing nematodes. Genome Res. 19(3):470–480. doi:10.1101/gr.081851.108.
Barton NH, Etheridge AM, Véber A. 2017. The infinitesimal model: definition, derivation, and implications. Theor Popul Biol. 118:50–73. doi:10.1016/j.tpb.2017.06.001.
Bateman AJ. 1948. Intra-sexual selection in *Drosophila*. Heredity (Edinb). 2(Pt 3):349–368. doi:10.1038/hdy.1948.21.
Baugh LR, Day T. 2020. Nongenetic inheritance and multigenerational plasticity in the nematode *C. elegans*. Elife. 9:e58498. doi:10.7554/eLife.58498.
Baugh LR, Hu PJ. 2020. Starvation responses throughout the *Caenorhabditis elegans* life cycle. Genetics. 216(4):837–878. doi:10.1534/genetics.120.303565.

Bayersdorf R, Schumacher B. 2019. Recent advances in understanding the mechanisms determining longevity. F1000Res. 8:F1000 Faculty Rev-1403. doi:10.12688/f1000research.19610.1.

Bell G, Koufopanou V. 1986. The cost of reproduction. Oxf Surv Evol Biol. 3:83–131.

Ben-David E, Pliota P, Widen SA, Koreshova A, Lemus-Vergara T, Verpukhovskiy P, Mandali S, Braendle C, Burga A, Kruglyak L. 2021. Ubiquitous selfish toxin-antidote elements in Caenorhabditis species. Curr Biol. 31(5):990–1001.e5. doi:10.1016/j.cub.2020.12.013.

Bergelson J, Kreitman M, Petrov DA, Sanchez A, Tikhonov M. 2021. Functional biology in its natural context: a search for emergent simplicity. Elife. 10:e67646. doi:10.7554/eLife.67646.

Bernstein MR, Zdraljevic S, Andersen EC, Rockman MV. 2019. Tightly linked antagonistic-effect loci underlie polygenic phenotypic variation in *C. elegans*. Evol Lett. 3(5):462–473. doi:10.1002/evl3.139.

Bever BW, Dietz ZP, Sullins JA, Montoya AM, Bergthorsson U, Katju V, Estes S. 2022. Mitonuclear mismatch is associated with increased male frequency, outcrossing, and male sperm size in experimentally-evolved *C. elegans*. Front Genet. 13:742272. doi:10.3389/fgene.2022.742272.

Billard B, Vigne P, Braendle C. 2020. A natural mutational event uncovers a life history trade-off via hormonal pleiotropy. Curr Biol. 30(21):4142–4154.e9. doi:10.1016/j.cub.2020.08.004.

Blaxter M, Koutsovoulos G. 2014. The evolution of parasitism in Nematoda. Parasitology. 142(Suppl 1):S26–S39. doi:10.1017/S0031182014000791.

Blaxter ML, Ley PD, Garey JR, Liu LX, Scheldeman P, Vierstraete A, Vanfleteren JR, Mackey LY, Dorris M, Frisse LM, *et al.* 1998. A molecular evolutionary framework for the phylum Nematoda. Nature. 392(6671):71–75. doi:10.1038/32160.

Boehm M, Slack F. 2005. A developmental timing microRNA and its target regulate life span in *C. elegans*. Science. 310(5756):1954–1957. doi:10.1126/science.1115596.

Bourg S, Jacob L, Menu F, Rajon E. 2019. Hormonal pleiotropy and the evolution of allocation trade-offs. Evolution. 73(4):661–674. doi:10.1111/evo.13693.

Boyle EA, Li YI, Pritchard JK. 2017. An expanded view of complex traits: from polygenic to omnigenic. Cell. 169(7):1177–1186. doi:10.1016/j.cell.2017.05.038.

Brady SC, Zdraljevic S, Bisaga KW, Tanny RE, Cook DE, Lee D, Wang Y, Andersen EC. 2019. A novel gene underlies bleomycin-response variation in *Caenorhabditis elegans*. Genetics. 212(4):1453–1468. doi:10.1534/genetics.119.302286.

Braendle C, Heyland A, Flatt T. 2011. Integrating mechanistic and evolutionary analysis of life history variation. Oxford University Press.

Braendle C, Milloz J, Félix M-A. 2008. Mechanisms and evolution of environmental responses in *Caenorhabditis elegans*. Curr Top Dev Biol. 80:171–207. doi:10.1016/S0070-2153(07)80005-6.

Brenner S. 1974. The genetics of *Caenorhabditis elegans*. Genetics. 77(1):71–94. doi:10.1093/genetics/77.1.71.

Briga M, Verhulst S. 2015. What can long-lived mutants tell us about mechanisms causing aging and lifespan variation in natural environments? Exp Gerontol. 71:21–26. doi:10.1016/j.exger.2015.09.002.

Brooks A, Lithgow GJ, Johnson TE. 1994. Mortality rates in a genetically heterogeneous population of *Caenorhabditis elegans*. Science. 263(5147):668–671. doi:10.1126/science.8303273.

Brown BC, Price AL, Patsopoulos NA, Zaitlen N. 2016. Local joint testing improves power and identifies hidden heritability in association studies. Genetics. 203(3):1105–1116. doi:10.1534/genetics.116.188292.

Burton NO, Riccio C, Dallaire A, Price J, Jenkins B, Koulman A, Miska EA. 2020. Cysteine synthases CYSL-1 and CYSL-2 mediate *C. elegans* heritable adaptation to *P. vranovensis* infection. Nat Commun. 11(1):1741. doi:10.1038/s41467-020-15555-8.

Burton NO, Willis A, Fisher K, Braukmann F, Price J, Stevens L, BaughLR, Reinke A, Miska EA. 2021. Intergenerational adaptations to stress are evolutionarily conserved, stress-specific, and have deleterious trade-offs. Elife. 10:e73425. doi:10.7554/eLife.73425.

Byerly L, Cassada RC, Russell RL. 1976. The life cycle of the nematode *Caenorhabditis elegans*. I. Wild-type growth and reproduction. Dev Biol. 51(1):23–33. doi:10.1016/0012-1606(76)90119-6.

Campbell RF, Mcgrath PT, Paaby AB. 2018. Analysis of epistasis in natural traits using model organisms. Trends Genet. 34(11):883–898. doi:10.1016/j.tig.2018.08.002.

Cao M. 2023. CRISPR-Cas9 genome editing in Steinernema entomopathogenic nematodes. bioRxiv 2023.11.24.568619. https://doi.org/10.1101/2023.11.24.568619, preprint: not peer reviewed

Carey JR. 2001. Insect biodemography. Annu Rev Entomol. 46(1):79–110. doi:10.1146/annurev.ento.46.1.79.

Carvalho S, Phillips PC, Teotónio H. 2014. Hermaphrodite life history and the maintenance of partial selfing in experimental populations of *Caenorhabditis elegans*. BMC Evol Biol. 14:117. doi:10.1186/1471-2148-14-117.

Cassada RC, Russell RL. 1975. The dauer larva, a post-embryonic developmental variant of the nematode *Caenorhabditis elegans*. Dev Biol. 46:326–342. doi:10.1016/0012-1606(75)90109-8.

Castagnone-Sereno P, Danchin EGJ, Perfus-Barbeoch L, Abad P. 2013. Diversity and evolution of root-knot nematodes, genus Meloidogyne: new insights from the genomic era. Annu Rev Phytopathol. 51:203–220. doi:10.1146/annurev-phyto-082712-102300.

Chapman H, Hsiung KC, Rawlinson I, Galimov ER, Gems D. 2024. Colony level fitness analysis identifies a trade-off between population growth rate and dauer yield in *Caenorhabditis elegans*. BMC Ecol Evol. 24(1):13. doi:10.1186/s12862-024-02199-1.

Charlesworth B. 1994. Evolution in age-structured populations. Cambridge University Press.

Charlesworth D, Willis JH. 2009. The genetics of inbreeding depression. Nat Rev Genet. 10(11):783–796. doi:10.1038/nrg2664.

Charnov EL. 1982. The theory of sex allocation. Princeton University Press. p. 1–355.

Chasnov JR. 2011. Evolution of increased self-sperm production in postdauer hermaphroditic nematodes. Evolution. 65(7):2117–2122. doi:10.1111/j.1558-5646.2011.01272.x.

Chebib J, Guillaume F. 2017. What affects the predictability of evolutionary constraints using a G-matrix? The relative effects of modular pleiotropy and mutational correlation. Evolution. 71(10):2298–2312. doi:10.1111/evo.13320.

Chelo IM, Teotónio H. 2013. The opportunity for balancing selection in experimental populations of *Caenorhabditis elegans*. Evolution. 67(1):142–156. doi:10.1111/j.1558-5646.2012.01744.x.

Chen J, Caswell-Chen EP. 2003. Why *Caenorhabditis elegans* adults sacrifice their bodies to progeny. Nematology. 5(4):641–645. doi:10.1163/156854103322683355.

Chen J, Caswell-Chen EP. 2004. Facultative vivipary is a life-history trait in *Caenorhabditis elegans*. J Nematol. 36(2):107–113.

Chen J, Lewis EE, Carey JR, Caswell H, Caswell-Chen EP. 2006. The ecology and biodemography of *Caenorhabditis elegans*. Exp Gerontol. 41(10):1059–1065. doi:10.1016/j.exger.2006.07.005.

Chen J, Senturk D, Wang JL, Müller HG, Carey JR, Caswell H, Caswell-Chen EP. 2007. A demographic analysis of the fitness cost of extended longevity in *Caenorhabditis elegans*. J Gerontol A Biol Sci Med Sci. 62(2):126. doi:10.1093/gerona/62.2.126.

Cheverud JM. 1988. A comparison of genetic and phenotypic correlations. Evolution. 42(5):958–968. doi:10.2307/2408911.

Cheverud JM, Routman EJ. 1995. Epistasis and its contribution to genetic variance components. Genetics. 139(3):1455–1461. doi:10.1093/genetics/139.3.1455.

Collins JB, Andersen EC. 2023. The Turkey ascarid, *Ascaridia dissimilis*, as a model genetic system. Int J Parasitol. 53(8):405–409. doi:10.1016/j.ijpara.2022.10.005.

Cook DE, Zdraljevic S, Roberts JP, Andersen EC. 2017. CeNDR, the *Caenorhabditis elegans* natural diversity resource. Nucleic Acids Res. 45(D1):D650–D657. doi:10.1093/nar/gkw893.

Crombie TA, Battlay P, Tanny RE, Evans KS, Buchanan CM, Cook DE, Dilks CM, Stinson LA, Zdraljevic S, Zhang G, *et al.* 2022. Local adaptation and spatiotemporal patterns of genetic diversity revealed by repeated sampling of *Caenorhabditis elegans* across the Hawaiian Islands. Mol Ecol. 31(8):2327–2347. doi:10.1111/mec.16400.

Crombie TA, McKeown R, Moya ND, Evans KS, Widmayer SJ, LaGrassa V, Roman N, Tursunova O, Zhang G, Gibson SB, *et al.* 2024. CaeNDR, the *Caenorhabditis* natural diversity resource. Nucleic Acids Res. 52(D1):D850–D858. doi:10.1093/nar/gkad887.

Crombie TA, Zdraljevic S, Cook DE, Tanny RE, Brady SC, Wang Y, Evans KS, Hahnel S, Lee D, Rodriguez BC, *et al.* 2019. Deep sampling of Hawaiian *Caenorhabditis elegans* reveals high genetic diversity and admixture with global populations. Elife. 8:e50465. doi:10.7554/eLife.50465.

Crook M. 2014. The dauer hypothesis and the evolution of parasitism: 20 years on and still going strong. Int J Parasitol. 44(1):1–8. doi:10.1016/j.ijpara.2013.08.004.

Cutter AD. 2004. Sperm-limited fecundity in nematodes: how many sperm are enough? Evolution. 58(3):651–655.

Cutter AD. 2006. Nucleotide polymorphism and linkage disequilibrium in wild populations of the partial selfer *Caenorhabditis elegans*. Genetics. 172(1):171–184. doi:10.1534/genetics.105.048207.

Cutter AD. 2015. *Caenorhabditis* evolution in the wild. Bioessays. 37(9):983–995. doi:10.1002/bies.201500053.

Cutter AD, Morran LT, Phillips PC. 2019. Males, outcrossing, and sexual selection in *Caenorhabditis* nematodes. Genetics. 213(1):27–57. doi:10.1534/genetics.119.300244.

Cutter AD, Payseur BA. 2003. Selection at linked sites in the partial selfer *Caenorhabditis elegans*. Mol Biol Evol. 20(5):665–673. doi:10.1093/molbev/msg072.

Daigle AT, Deiss TC, Melde RH, Bergthorsson U, Katju V. 2022. Bergerac strains of *C. elegans* revisited: expansion of tc1 elements impose a significant genomic and fitness cost. G3 (Bethesda). 12(11):jkac214. doi:10.1093/g3journal/jkac214

David JR, Capy P. 1988. Genetic variation of *Drosophila melanogaster* natural populations. Trends Genet. 4(4):106–111. doi:10.1016/0168-9525(88)90098-4.

Davies EK, Peters AD, Keightley PD. 1999. High frequency of cryptic deleterious mutations in *Caenorhabditis elegans*. Science. 285(5434):1748–1751. doi:10.1126/science.285.5434.1748.

Dayi M, Kanzaki N, Sun S, Ide T, Tanaka R, Masuya H, Okabe K, Kajimura H, Kikuchi T. 2021. Additional description and genome analyses of *Caenorhabditis auriculariae* representing the basal lineage of genus Caenorhabditis. Sci Rep. 11(1):6720. doi:10.1038/s41598-021-85967-z.

De Chiara M, Barré BP, Persson K, Irizar A, Vischioni C, Khaiwal S, Stenberg S, Amadi OC, Žun G, Doberšek K, *et al.* 2022. Domestication reprogrammed the budding yeast life cycle. Nat Ecol Evol. 6(4):448–460. doi:10.1038/s41559-022-01671-9.

De Ley P. 2006. A quick tour of nematode diversity and the backbone of nematode phylogeny. WormBook. 1–8. doi:10.1895/wormbook.1.41.1.

De Ley P, Blaxter ML. 2004. A new system for Nematoda: combining morphological characters with molecular trees, and translating clades into ranks and taxa. In: *Proceedings of the Fourth International Congress of Nematology. Nematology Monographs and Perspectives*, Volume 2; Tenerife, Spain. Brill. p. 633–653.

Denver DR, Clark KA, Raboin MJ. 2011. Reproductive mode evolution in nematodes: insights from molecular phylogenies and recently discovered species. Mol Phylogenet Evol. 61(2):584–592. doi:10.1016/j.ympev.2011.07.007.

Denver DR, Morris K, Lynch M, Vassilieva LL, Thomas WK. 2000. High direct estimate of the mutation rate in the mitochondrial genome of *Caenorhabditis elegans*. Science. 289(5488):2342–2344. doi:10.1126/science.289.5488.2342.

Dey A, Chan CKW, Thomas CG, Cutter AD. 2013. Molecular hyperdiversity defines populations of the nematode *Caenorhabditis brenneri*. Proc Natl Acad Sci U S A. 110(27):11056–11060. doi:10.1073/pnas.1303057110.

Dey A, Jeon Y, Wang G-X, Cutter AD. 2012. Global population genetic structure of *Caenorhabditis remanei* reveals incipient speciation. Genetics. 191(4):1257–1269. doi:10.1534/genetics.112.140418.

Dey S, Proulx SR, Teotónio H. 2016. Adaptation to temporally fluctuating environments by the evolution of maternal effects. PLoS Biol. 14(2):e1002388. doi:10.1371/journal.pbio.1002388.

Diaz SA, Lindström J, Haydon DT. 2008. Basic demography of *Caenorhabditis remanei* cultured under standard laboratory conditions. J Nematol. 40(3):167–178.

Diaz SA, Viney M. 2015. The evolution of plasticity of dauer larva developmental arrest in the nematode *Caenorhabditis elegans*. Ecol Evol. 5(6):1343–1353. doi:10.1002/ece3.1436.

Dickinson DJ, Goldstein B. 2016. CRISPR-based methods for *Caenorhabditis elegans* genome engineering. Genetics. 202(3):885–901. doi:10.1534/genetics.115.182162.

Dillin A, Crawford DK, Kenyon C. 2002. Timing requirements for insulin/IGF-1 signaling in *C. elegans*. Science. 298(5594):830–834. doi:10.1126/science.1074240.

Dirksen P, Assié A, Zimmermann J, Zhang F, Tietje A-M, Marsh SA, Félix M-A, Shapira M, Kaleta C, Schulenburg H, *et al.* 2020. CeMbio—the *Caenorhabditis elegans* microbiome resource. G3 (Bethesda). 10(9):3025–3039. doi:10.1534/g3.120.401309.

Doebley JF, Gaut BS, Smith BD. 2006. The molecular genetics of crop domestication. Cell. 127(7):1309–1321. doi:10.1016/j.cell.2006.12.006.

Doitsidou M, Jarriault S, Poole RJ. 2016. Next-generation sequencing-based approaches for mutation mapping and identification in *Caenorhabditis elegans*. Genetics. 204(2):451–474. doi:10.1534/genetics.115.186197.

Dolgin ES, Charlesworth B, Baird SE, Cutter AD. 2007. Inbreeding and outbreeding depression in Caenorhabditis nematodes. Evolution. 61(6):1339–1352. doi:10.1111/j.1558-5646.2007.00118.x.

Driscoll CA, Macdonald DW, O'Brien SJ. 2009. From wild animals to domestic pets, an evolutionary view of domestication. Proc Natl Acad Sci U S A. 106(Suppl 1):9971–9978. doi:10.1073/pnas.0901586106.

Duveau F, Félix M-A. 2012. Role of pleiotropy in the evolution of a cryptic developmental variation in *Caenorhabditis elegans*. PLoS Biol. 10(1):e1001230. doi:10.1371/journal.pbio.1001230.

Ebert RH II, Cherkasova VA, Dennis RA, Wu JH, Ruggles S, Perrin TE, Shmookler Reis RJ. 1993. Longevity-determining genes in *Caenorhabditis elegans*: chromosomal mapping of multiple noninteractive loci. Genetics. 135(4):1003–1010. doi:10.1093/genetics/135.4.1003.

Ellis RE. 2010. The sperm/oocyte decision, a *C. elegans* perspective. In: Verlhac MH, Villeneuve A, editors. Oogenesis: the universal process. Wiley. doi:10.1002/9780470687970.ch1.

Ellis RE. 2022. Sex determination in nematode germ cells. Sex Dev. 16(5–6):305–322. doi:10.1159/000520872

Ellis RE, Lin S-Y. 2014. The evolutionary origins and consequences of self-fertility in nematodes. F1000Prime Rep. 6:62. doi:10.12703/P6-62.
Estes S, Ajie BC, Lynch M, Phillips PC. 2005. Spontaneous mutational correlations for life-history, morphological and behavioral characters in *Caenorhabditis elegans*. Genetics. 170(2):645–653. doi:10.1534/genetics.104.040022.
Estes S, Coleman-Hulbert AL, Hicks KA, de Haan G, Martha SR, Knapp JB, Smith SW, Stein KC, Denver DR. 2011. Natural variation in life history and aging phenotypes is associated with mitochondrial DNA deletion frequency in *Caenorhabditis briggsae*. BMC Evol Biol. 11:11. doi:10.1186/1471-2148-11-11.
Estes S, Dietz ZP, Katju V, Bergthorsson U. 2023. Evolutionary co-dependency: insights into the mitonuclear interaction landscape from experimental and wild Caenorhabditis nematodes. Curr Opin Genet Dev. 81:102081. doi:10.1016/j.gde.2023.102081.
Evans KS, van Wijk MH, Mcgrath PT, Andersen EC, Sterken MG. 2021. From QTL to gene: *C. elegans* facilitates discoveries of the genetic mechanisms underlying natural variation. Trends Genet. 37(10):933–947. doi:10.1016/j.tig.2021.06.005.
Evans KS, Zhao Y, Brady SC, Long L, Mcgrath PT, Andersen EC. 2017. Correlations of genotype with climate parameters suggest *Caenorhabditis elegans* niche adaptations. G3 (Bethesda). 7(1):289–298. doi:10.1534/g3.116.035162.
Eyre-Walker A. 2010. Genetic architecture of a complex trait and its implications for fitness and genome-wide association studies. Proc Natl Acad Sci U S A. 107(Suppl 1):1752–1756. doi:10.1073/pnas.0906182107.
Fagny M, Austerlitz F. 2021. Polygenic adaptation: integrating population genetics and gene regulatory networks. Trends Genet. 37(7):631–638. doi:10.1016/j.tig.2021.03.005.
Falconer DS, Mackay TFC. 1996. Introduction to quantitative genetics. Addison Wesley Longman.
Farhadifar R, Baer CF, Valfort A-C, Andersen EC, Müller-Reichert T, Delattre M, Needleman DJ. 2015. Scaling, selection, and evolutionary dynamics of the mitotic spindle. Curr Biol. 25(6):732–740. doi:10.1016/j.cub.2014.12.060.
Fatt HV, Dougherty EC. 1963. Genetic control of differential heat tolerance in two strains of the nematode *Caenorhabditis elegans*. Science. 141(3577):266–267. doi:10.1126/science.141.3577.266.
Fausett S, Poullet N, Gimond C, Vielle A, Bellone M, Braendle C. 2021. Germ cell apoptosis is critical to maintain *Caenorhabditis elegans* offspring viability in stressful environments. PLoS One. 16(12):e0260573. doi:10.1371/journal.pone.0260573.
Fausett SR, Sandjak A, Billard B, Braendle C. 2023. Higher-order epistasis shapes natural variation in germ stem cell niche activity. Nat Commun. 14(1):2824. doi:10.1038/s41467-023-38527-0.
Félix M-A. 2004. Alternative morphs and plasticity of vulval development in a rhabditid nematode species. Dev Genes Evol. 214(2):55–63. doi:10.1007/s00427-003-0376-y.
Félix M-A, Braendle C. 2010. The natural history of *Caenorhabditis elegans*. Curr Biol. 20:R965–R969. doi:10.1016/j.cub.2010.09.050.
Félix M-A, Braendle C, Cutter AD. 2014. A streamlined system for species diagnosis in Caenorhabditis (Nematoda: Rhabditidae) with name designations for 15 distinct biological species. PLoS One. 9(4):e94723. doi:10.1371/journal.pone.0094723.
Félix M-A, Duveau F. 2012. Population dynamics and habitat sharing of natural populations of *Caenorhabditis elegans* and *C. briggsae*. BMC Biol. 10:59. doi:10.1186/1741-7007-10-59.
Ferrari C, Salle R, Callemeyn-Torre N, Jovelin R, Cutter AD, Braendle C. 2017. Ephemeral-habitat colonization and neotropical species richness of Caenorhabditis nematodes. BMC Ecol. 17(1):43. doi:10.1186/s12898-017-0150-z.
Fielenbach N, Antebi A. 2008. *C. elegans* dauer formation and the molecular basis of plasticity. Genes Dev. 22(16):2149–2165. doi:10.1101/gad.1701508.
Finch CE, Rose MR. 1995. Hormones and the physiological architecture of life history evolution. Q Rev Biol. 70(1):1–52. doi:10.1086/418864.
Fisher RA. 1918. The correlation between relatives on the supposition of mendelian inheritance. Earth Environ Sci Trans R Soc Edinb. 52:399–433. doi:10.1017/S0080456800012163.
Fisher RA. 1930. The genetical theory of natural selection. Clarendon Press.
Flatt T. 2020. Life-history evolution and the genetics of fitness components in *Drosophila melanogaster*. Genetics. 214(1):3–48. doi:10.1534/genetics.119.300160.
Flatt T, Heyland A. 2011. Mechanisms of life history evolution: the genetics and physiology of life history traits and trade-offs. Oxford University Press.
Frézal L, Demoinet E, Braendle C, Miska E, Félix M-A. 2018. Natural genetic variation in a multigenerational phenotype in *C. elegans*. Curr Biol. 28(16):2588–2596.e8. doi:10.1016/j.cub.2018.05.091.
Frezal L, Félix M-A. 2015. *C. elegans* outside the Petri dish. Elife. 4:e05849 doi:10.7554/eLife.05849.
Friedman DB, Johnson TE. 1988. A mutation in the age-1 gene in *Caenorhabditis elegans* lengthens life and reduces hermaphrodite fertility. Genetics. 118(1):75–86. doi:10.1093/genetics/118.1.75.
Futuyma DJ, Moreno G. 1988. The evolution of ecological specialization. Annu Rev Ecol Syst. 19:207–233. doi:10.1146/annurev.es.19.110188.001231.
Gaertner BE, Parmenter MD, Rockman MV, Kruglyak L, Phillips PC. 2012. More than the sum of its parts: a Complex epistatic network underlies natural variation in thermal preference behavior in *Caenorhabditis elegans*. Genetics. 192(4):1533–1542. doi:10.1534/genetics.112.142877.
Gaertner BE, Phillips PC. 2010. *Caenorhabditis elegans* as a platform for molecular quantitative genetics and the systems biology of natural variation. Genet Res (Camb). 92(5-6):331–348. doi:10.1017/S0016672310000601.
Galimov ER, Gems D. 2020. Shorter life and reduced fecundity can increase colony fitness in virtual *Caenorhabditis elegans*. Aging Cell. 19(5):e13141. doi:10.1111/acel.13141
Gao AW, Sterken MG, de Bos JU, van Creij J, Kamble R, Snoek BL, Kammenga JE, Houtkooper RH. 2018. Natural genetic variation in *C. elegans* identified genomic loci controlling metabolite levels. Genome Res. 28(9):1296–1308. doi:10.1101/gr.232322.117.
Garland T, Rose MR. 2009. Experimental evolution: concepts, methods, and applications of selection experiments. University of California Press.
Gems D, Riddle DL. 1996. Longevity in *Caenorhabditis elegans* reduced by mating but not gamete production. Nature. 379(6567):723–725. doi:10.1038/379723a0.
Gerisch B, Rottiers V, Li D, Motola DL, Cummins CL, Lehrach H, Mangelsdorf DJ, Antebi A 2007. A bile acid-like steroid modulates *Caenorhabditis elegans* lifespan through nuclear receptor signaling. Proc Natl Acad Sci U S A. 104(12):5014–5019. doi:10.1073/pnas.0700847104.
Gerisch B, Tharyan RG, Mak J, Denzel SI, Popkes-van Oepen T, Henn N, Antebi A. 2020. HLH-30/TFEB is a master regulator of reproductive quiescence. Dev Cell. 53(3):316–329.e5. doi:10.1016/j.devcel.2020.03.014.
Gerisch B, Weitzel C, Kober-Eisermann C, Rottiers V, Antebi A. 2001. A hormonal signaling pathway influencing *C. elegans* metabolism, reproductive development, and life span. Dev Cell. 1(6):841–851. doi:10.1016/S1534-5807(01)00085-5.

Gilabert A, Curran DM, Harvey SC, Wasmuth JD. 2016. Expanding the view on the evolution of the nematode dauer signalling pathways: refinement through gene gain and pathway co-option. BMC Genomics. 17(Supp 1):1. doi:10.1186/s12864-015-2294-6.

Gilbert KJ, Zdraljevic S, Cook DE, Cutter AD, Andersen EC, Baer CF. 2022. The distribution of mutational effects on fitness in *Caenorhabditis elegans* inferred from standing genetic variation. Genetics. 220(1):iyab166. doi:10.1093/genetics/iyab166.

Gillespie JH, Turelli M. 1989. Genotype-environment interactions and the maintenance of polygenic variation. Genetics. 121(1): 129–138. doi:10.1093/genetics/121.1.129.

Gimond C, Vielle A, Silva-Soares N, Zdraljevic S, Mcgrath PT, Andersen EC, Braendle C. 2019. Natural variation and genetic determinants of *Caenorhabditis elegans* sperm size. Genetics. 213(2): 615–632. doi:10.1534/genetics.119.302462.

Glater EE, Rockman MV, Bargmann CI. 2014. Multigenic natural variation underlies *Caenorhabditis elegans* olfactory preference for the bacterial pathogen *Serratia marcescens*. G3 (Bethesda). 4(2):265–276. doi:10.1534/g3.113.008649.

Gloria-Soria A, Azevedo RBR. 2008. npr-1 regulates foraging and dispersal strategies in *Caenorhabditis elegans*. Curr Biol. 18(21): 1694–1699. doi:10.1016/j.cub.2008.09.043.

Golden JW, Riddle DL. 1982. A pheromone influences larval development in the nematode *Caenorhabditis elegans*. Science 218(4572): 578–580. doi:10.1126/science.6896933.

Gray JC, Cutter AD. 2014. Mainstreaming *Caenorhabditis elegans* in experimental evolution. Proc R Soc Lond B Biol Sci. 281(1778): 20133055. doi:10.1098/rspb.2013.3055.

Green JWM, Snoek LB, Kammenga JE, Harvey SC. 2013. Genetic mapping of variation in dauer larvae development in growing populations of *Caenorhabditis elegans*. Heredity (Edinb). 111(4):306–313. doi:10.1038/hdy.2013.50.

Green JWM, Stastna JJ, Orbidans HE, Harvey SC. 2014. Highly polygenic variation in environmental perception determines dauer larvae formation in growing populations of *Caenorhabditis elegans*. PLoS One. 9(11):e112830. doi:10.1371/journal.pone.0112830.

Guo Y, Lang S, Ellis RE. 2009. Independent recruitment of F box genes to regulate hermaphrodite development during nematode evolution. Curr Biol. 19(21):1853–1860. doi:10.1016/j.cub.2009.09.042.

Gusarov I, Gautier L, Smolentseva O, Shamovsky I, Eremina S, Mironov A, Nudler E. 2013. Bacterial nitric oxide extends the lifespan of *C. elegans*. Cell. 152(4):818–830. doi:10.1016/j.cell.2012.12.043.

Gutteling EW, Doroszuk A, Riksen JAG, Prokop Z, Reszka J, Kammenga JE. 2007. Environmental influence on the genetic correlations between life-history traits in *Caenorhabditis elegans*. Heredity (Edinb). 98(4):206–213. doi:10.1038/sj.hdy.6800929.

Gutteling EW, Riksen JAG, Bakker J, Kammenga JE. 2007. Mapping phenotypic plasticity and genotype-environment interactions affecting life-history traits in *Caenorhabditis elegans*. Heredity (Edinb). 98(1):28–37. doi:10.1038/sj.hdy.6800894.

Guzella TS, Dey S, Chelo IM, Pino-Querido A, Pereira VF, Proulx SR, Teotónio H. 2018. Slower environmental change hinders adaptation from standing genetic variation. PLoS Genet. 14(11): e1007731. doi:10.1371/journal.pgen.1007731.

Haag ES, Chamberlin H, Coghlan A, Fitch DHA, Peters AD, Schulenburg H. 2007. *Caenorhabditis* evolution: if they all look alike, you aren't looking hard enough. Trends Genet. 23(3): 101–104. doi:10.1016/j.tig.2007.01.002.

Haag ES, Fitch DHA, Delattre M. 2018. From "the worm" to "the worms" and back again: the evolutionary developmental biology of nematodes. Genetics. 210(2):397–433. doi:10.1534/genetics.118.300243.

Haber M, Schüngel M, Putz A, Müller S, Hasert B, Schulenburg H. 2005. Evolutionary history of *Caenorhabditis elegans* inferred from microsatellites: evidence for spatial and temporal genetic differentiation and the occurrence of outbreeding. Mol Biol Evol. 22(1):160–173. doi:10.1093/molbev/msh264.

Hallem EA, Rengarajan M, Ciche TA, Sternberg PW. 2007. Nematodes, bacteria, and flies: a tripartite model for nematode parasitism. Curr Biol. 17(10):898–904. doi:10.1016/j.cub.2007.04.027.

Hamilton WD. 1967. Extraordinary sex ratios. A sex-ratio theory for sex linkage and inbreeding has new implications in cytogenetics and entomology. Science. 156(3774):477–488. doi:10.1126/science.156.3774.477.

Harvey SC, Alison S, Viney ME. 2008. Quantitative genetic analysis of life-history traits of caenorhabditis elegans in stressful environments. BMC Evol Biol. 8:15.

Harvey SC, Orbidans HE. 2011. All eggs are not equal: the maternal environment affects progeny reproduction and developmental fate in *Caenorhabditis elegans*. PLoS One. 6(10):e25840. doi:10.1371/journal.pone.0025840.

Harvey PH, Pagel MD. 1998. The comparative method in evolutionary biology. Oxford University Press.

Harvey SC, Viney ME. 2007. Thermal variation reveals natural variation between isolates of *Caenorhabditis elegans*. J Exp Zool B Mol Dev Evol. 308(5):409–416. doi:10.1002/jez.b.21161.

Henderson ST, Johnson TE. 2001. daf-16 integrates developmental and environmental inputs to mediate aging in the nematode *Caenorhabditis elegans*. Curr Biol. 11(24):1975–1980. doi:10.1016/S0960-9822(01)00594-2.

Hibshman JD, Hung A, Baugh LR. 2016. Maternal diet and insulin-like signaling control intergenerational plasticity of progeny size and starvation resistance. PLoS Genet. 12(10):e1006396. doi:10.1371/journal.pgen.1006396.

Hirsh D, Oppenheim D, Klass M. 1976. Development of the reproductive system of *Caenorhabditis elegans*. Dev Biol. 49(1):200–219. doi:10.1016/0012-1606(76)90267-0.

Hitchcock TJ, Gardner A. 2023. Sexual antagonism in sequential hermaphrodites. Proc Biol Sci. 290(2011):20232222. doi:10.1098/rspb.2023.2222.

Hodda M. 2022. Phylum Nematoda: a classification, catalogue and index of valid genera, with a census of valid species. Zootaxa. 5114(1):1–289. doi:10.11646/zootaxa.5114.1.1.

Hodgkin J, Barnes TM. 1991. More is not better: brood size and population growth in a self-fertilizing nematode. Proc Biol Sci. 246(1315):19–24. doi:10.1098/rspb.1991.0119.

Hodgkin J, Doniach T. 1997. Natural variation and copulatory plug formation in *Caenorhabditis elegans*. Genetics. 146(1):149–164. doi:10.1093/genetics/146.1.149.

Houle D. 1991. Genetic covariance of fitness correlates: what genetic correlations are made of and why it matters. Evolution. 45(3): 630–648. doi:10.2307/2409916.

Houle D. 1992. Comparing evolvability and variability of quantitative traits. Genetics. 130(1):195–204. doi:10.1093/genetics/130.1.195.

Hsin H, Kenyon C. 1999. Signals from the reproductive system regulate the lifespan of *C. elegans*. Nature. 399(6734):362–366. doi:10.1038/20694.

Hu PJ. 2007. Dauer. Wormbook. 1–19. doi:10.1895/wormbook.1.144.1.

Huang Y, Lo Y-H, Hsu J-C, Le TS, Yang F-J, Chang T, Braendle C, Wang J. 2023. Widespread sex ratio polymorphism in Caenorhabditis nematodes. R Soc Open Sci. 10(3):221636. doi:10.1098/rsos.221636.

Hubbard EJA, Schedl T. 2019. Biology of the *Caenorhabditis elegans* germline stem cell system. Genetics. 213(4):1145–1188. doi:10.1534/genetics.119.300238.

Hughes KA, Leips J. 2016. Pleiotropy, constraint, and modularity in the evolution of life histories: insights from genomic analyses. Ann N Y Acad Sci. 1389(1):76–91. doi:10.1111/nyas.13256.

Jenkins NL, McColl G, Lithgow GJ. 2004. Fitness cost of extended lifespan in *Caenorhabditis elegans*. Proc Biol Sci. 271(1556):2523–2526. doi:10.1098/rspb.2004.2897.

Jia K, Chen D, Riddle DL. 2004. The TOR pathway interacts with the insulin signaling pathway to regulate *C. elegans* larval development, metabolism and life span. Development. 131(16): 3897–3906. doi:10.1242/dev.01255.

Jobson MA, Jordan JM, Sandrof MA, Hibshman JD, Lennox AL, Baugh LR. 2015. Transgenerational effects of early life starvation on growth, reproduction, and stress resistance in *Caenorhabditis elegans*. Genetics. 201(1):201–212. doi:10.1534/genetics.115.178699.

Johnson TE, Hutchinson EW. 1993. Absence of strong heterosis for life span and other life history traits in *Caenorhabditis elegans*. Genetics. 134(2):465–474. doi:10.1093/genetics/134.2.465.

Johnson TE, Wood WB. 1982. Genetic analysis of life-span in *Caenorhabditis elegans*. Proc Natl Acad Sci U S A. 79(21):6603–6607. doi:10.1073/pnas.79.21.6603.

Jordan JM, Hibshman JD, Webster AK, Kaplan REW, Leinroth A, Guzman R, Maxwell CS, Chitrakar R, Bowman EA, Fry AL, *et al.* 2019. Insulin/IGF signaling and vitellogenin provisioning mediate intergenerational adaptation to nutrient stress. Curr Biol. 29(14): 23802388.e5. doi:10.1016/j.cub.2019.05.062.

Jordan JM, Webster AK, Chen J, Chitrakar R, Ryan Baugh L. 2023. Early-life starvation alters lipid metabolism in adults to cause developmental pathology in *Caenorhabditis elegans*. Genetics. 223(2): iyac172. doi:10.1093/genetics/iyac172.

Kammenga JE, Doroszuk A, Riksen JAG, Hazendonk E, Spiridon L, Petrescu A-J, Tijsterman M, Plasterk RHA, Bakker J. 2007. A *Caenorhabditis elegans* wild type defies the temperature–size rule owing to a single nucleotide polymorphism in tra-3. PLoS Genet. 3(3):e34. doi:10.1371/journal.pgen.0030034.

Kanzaki N, Kiontke K, Tanaka R, Hirooka Y, Schwarz A, Müller-Reichert T, Chaudhuri J, Pires-daSilva A. 2017. Description of two three-gendered nematode species in the new genus Auanema (Rhabditina) that are models for reproductive mode evolution. Sci Rep. 7(1):11135. doi:10.1038/s41598-017-09871-1.

Kanzaki N, Tsai IJ, Tanaka R, Hunt VL, Liu D, Tsuyama K, Maeda Y, Namai S, Kumagai R, Tracey A, *et al.* 2018. Biology and genome of a newly discovered sibling species of *Caenorhabditis elegans*. Nat Commun. 9(1):3216. doi:10.1038/s41467-018-05712-5.

Keightley PD, Caballero A. 1997. Genomic mutation rates for lifetime reproductive output and lifespan in *Caenorhabditis elegans*. Proc Natl Acad Sci U S A. 94(8):3823–3827. doi:10.1073/pnas.94.8.3823.

Kenyon C. 2005. The plasticity of aging: insights from long-lived mutants. Cell. 120(4):449–460. doi:10.1016/j.cell.2005.02.002.

Kenyon C. 2011. The first long-lived mutants: discovery of the insulin/IGF-1 pathway for ageing. Philos Trans R Soc Lond B Biol Sci. 366(1561):9–16. doi:10.1098/rstb.2010.0276.

Kenyon C, Chang J, Gensch E, Rudner A, Tabtiang R. 1993. A *C. elegans* mutant that lives twice as long as wild type. Nature. 366(6454): 461–464. doi:10.1038/366461a0.

Ketterson ED, Nolan V. 1992. Hormones and life histories: an integrative approach. Am Nat. 140(Suppl 1):S33–S62. doi:10.1086/285396.

Kim S, Paik Y-K. 2008. Developmental and reproductive consequences of prolonged non-aging dauer in *Caenorhabditis elegans*. Biochem Biophys Res Commun. 368(3):588–592. doi:10.1016/j.bbrc.2008.01.131.

Kimble J, Hirsh D. 1979. The postembryonic cell lineages of the hermaphrodite and male gonads in *Caenorhabditis elegans*. Dev Biol. 70(2):396–417. doi:10.1016/0012-1606(79)90035-6.

Kimura KD, Tissenbaum HA, Liu Y, Ruvkun G. 1997. daf-2, an insulin receptor-like gene that regulates longevity and diapause in *Caenorhabditis elegans*. Science. 277(5328):942–946. doi:10.1126/science.277.5328.942.

Kiontke K. 1997. Description of Rhabditis (Caenorhabditis) drosophilae n. sp. and R.(C.) sonorae n. sp.(Nematoda: Rhabditida) from saguaro cactus rot in Arizona. Fundam Appl Nematol. 20: 305–315.

Kiontke K. 2006. Ecology of Caenorhabditis species. WormBook. 1–14. doi:10.1895/wormbook.1.37.1.

Kiontke KC, Félix M-A, Ailion M, Rockman MV, Braendle C, Pénigault J-B, Fitch DHA. 2011. A phylogeny and molecular barcodes for Caenorhabditis, with numerous new species from rotting fruits. BMC Evol Biol. 11:339. doi:10.1186/1471-2148-11-339.

Kiontke K, Fitch DHA. 2005. The phylogenetic relationships of *Caenorhabditis* and other rhabditids. WormBook. 11:1–11. doi:10.1895/wormbook.1.11.1.

Kiontke K, Hironaka M, Sudhaus W. 2011. Description of *Caenorhabditis japonica* n. sp. (Nematoda: Rhabditida) associated with the burrower bug *Parastrachia japonensis* (Heteroptera: Cydnidae) in Japan. Nematology. 4:933–941. doi:10.1163/156854102321122557.

Kirkwood TB. 1977. Evolution of ageing. Nature. 270(5630):301–304. doi:10.1038/270301a0.

Klass MR. 1983. A method for the isolation of longevity mutants in the nematode *Caenorhabditis elegans* and initial results. Mech Ageing Dev. 22(3–4):279–286. doi:10.1016/0047-6374(83)90082-9.

Klass M, Hirsh D. 1976. Non-ageing developmental variant of *Caenorhabditis elegans*. Nature. 260(5551):523–525. doi:10.1038/260523a0.

Knight CG, Azevedo RB, Leroi AM. 2001. Testing life-history pleiotropy in *Caenorhabditis elegans*. Evolution. 55(9):1795–1804. doi:10.1111/j.0014-3820.2001.tb00828.x.

Korta DZ, Hubbard EJA. 2010. Soma-germline interactions that influence germline proliferation in *Caenorhabditis elegans*. Dev Dyn. 239(5):1449–1459. doi:10.1002/dvdy.22268.

Kreis HA. 1964. Ein neuer Nematode aus dem äusseren Gehörgang von Zeburindern in Ostafrika, Rhabditis bovis n. sp. (Rhabditidoidea; Rhabditidae). Schweiz Arch Tierh. 106:372–378.

Lack D. 1954. The Natural Regulation of Animal Numbers. Oxford (UK): Clarendon Press.

Lambshead PJD. 2004. Marine nematode biodiversity. In: Nematology: Advances and Perspectives. Volume 1: Nematode Morphology, Physiology, and Ecology. CABI Publishing. p. 438–468.

LaMunyon CW, Ward S. 1998. Larger sperm outcompete smaller sperm in the nematode *Caenorhabditis elegans*. Proc Biol Sci. 265(1409):1997–2002. doi:10.1098/rspb.1998.0531.

Large EE, Padmanabhan R, Watkins KL, Campbell RF, Xu W, McGrath PT. 2017. Modeling of a negative feedback mechanism explains antagonistic pleiotropy in reproduction in domesticated *Caenorhabditis elegans* strains. PLoS Genet. 13(5):e1006769. doi:10.1371/journal.pgen.1006769.

Large EE, Xu W, Zhao Y, Brady SC, Long L, Butcher RA, Andersen EC, McGrath PT. 2016. Selection on a subunit of the NURF chromatin remodeler modifies life history traits in a domesticated strain of *Caenorhabditis elegans*. PLoS Genet. 12(7):e1006219. doi:10.1371/journal.pgen.1006219.

Launay C, Félix M-A, Dieng J, Delattre M. 2020. Diversification and hybrid incompatibility in auto-pseudogamous species of Mesorhabditis nematodes. BMC Evol Biol. 20(1):1. doi:10.1186/s12862-019-1549-2.

Le KN, Zhan M, Cho Y, Wan J, Patel DS, Lu H. 2020. An automated platform to monitor long-term behavior and healthspan in

Caenorhabditis elegans under precise environmental control. Commun Biol. 3(1):297. doi:10.1038/s42003-020-1013-2.

Lee DL. 2002. The biology of nematodes. CRC Press.

Lee H, Choi M-K, Lee D, Kim H-S, Hwang H, Kim H, Park S, Paik Y-K, Lee J. 2012. Nictation, a dispersal behavior of the nematode *Caenorhabditis elegans*, is regulated by IL2 neurons. Nat Neurosci. 15(1):107–112. doi:10.1038/nn.2975.

Lee YW, Gould BA, Stinchcombe JR. 2014. Identifying the genes underlying quantitative traits: a rationale for the QTN programme. AoB Plants. 6:plu004. doi:10.1093/aobpla/plu004.

Lee D, Zdraljevic S, Cook DE, Frézal L, Hsu J-C, Sterken MG, Riksen JAG, Wang J, Kammenga JE, Braendle C, *et al.* 2019. Selection and gene flow shape niche-associated variation in pheromone response. Nat Ecol Evol. 3(10):1455–1463. doi:10.1038/s41559-019-0982-3.

Lee D, Zdraljevic S, Stevens L, Wang Y, Tanny RE, Crombie TA, Cook DE, Webster AK, Chirakar R, Baugh LR, *et al.* 2021. Balancing selection maintains hyper-divergent haplotypes in *Caenorhabditis elegans*. Nat Ecol Evol. 5(6):794–807. doi:10.1038/s41559-021-01435-x.

Lehtinen MK, Yuan Z, Boag PR, Yang Y, Villén J, Becker EBE, DiBacco S, de la Iglesia N, Gygi S, Blackwell TK, *et al.* 2006. A conserved MST-FOXO signaling pathway mediates oxidative-stress responses and extends life span. Cell. 125(5):987–1001. doi:10.1016/j.cell.2006.03.046.

Leonard JL. 2019. Transitions between sexual systems: understanding the mechanisms of, and pathways between, dioecy, hermaphroditism and other sexual systems. Springer. p. 1–363.

Leroi AM. 2001. Molecular signals versus the Loi de Balancement. Trends Ecol Evol. 16(1):24–29. doi:10.1016/S0169-5347(00)02032-2.

Leroi AM, Bartke A, Benedictis GD, Franceschi C, Gartner A, Gonos E, Feder ME, Kivisild T, Lee S, Kartal-Özer N, *et al.* 2005. What evidence is there for the existence of individual genes with antagonistic pleiotropic effects? Mech Ageing Dev. 126(3):421–429. doi:10.1016/j.mad.2004.07.012.

Lesaffre T, Billiard S. 2019. The joint evolution of lifespan and self-fertilization. J Evol Biol. 33(1):41–56. doi:10.1111/jeb.13543.

Lewis SC, Dyal LA, Hilburn CF, Weitz S, Liau W-S, Lamunyon CW, Denver DR. 2009. Molecular evolution in Panagrolaimus nematodes: origins of parthenogenesis, hermaphroditism and the Antarctic species *P. davidi*. BMC Evol Biol. 9:15. doi:10.1186/1471-2148-9-15.

Lewontin R. 1974. The genetic basis of evolutionary change. Columbia University Press.

Li S, Jovelin R, Yoshiga T, Tanaka R, Cutter AD. 2014. Specialist versus generalist life histories and nucleotide diversity in Caenorhabditis nematodes. Proc R Soc Lond B Biol Sci. 281(1777):20132858. doi:10.1098/rspb.2013.2858.

Lim J, Kim J, Lee J. 2021. Natural variation in reproductive timing and X-chromosome non-disjunction in *Caenorhabditis elegans*. G3 (Bethesda). 11(12):jkab327. doi:10.1093/g3journal/jkab327.

Lin K, Dorman JB, Rodan A, Kenyon C. 1997. daf-16: an HNF-3/forkhead family member that can function to double the life-span of *Caenorhabditis elegans*. Science. 278(5349):1319–1322. doi:10.1126/science.278.5341.1319.

Lints R, Emmons SW. 2002. Regulation of sex-specific differentiation and mating behavior in *C. elegans* by a new member of the DM domain transcription factor family. Genes Dev. 16:2390–2402. doi:10.1101/gad.1012602.

Liu C, Grote A, Ghedin E, Unnasch TR. 2020. CRISPR-mediated Transfection of *Brugia malayi*. PLoS Negl Trop Dis. 14(8):e0008627. doi:10.1371/journal.pntd.0008627.

Lohr JN, Galimov ER, Gems D. 2019. Does senescence promote fitness in *Caenorhabditis elegans* by causing death? Ageing Res Rev. 50:58–71. doi:10.1016/j.arr.2019.01.008.

Long L, Xu W, Valencia F, Paaby AB, McGrath PT. 2023. A toxin-antidote selfish element increases fitness of its host. Elife. 12:e81640. doi:10.7554/eLife.81640.

Ludewig AH, Artyukhin AB, Aprison EZ, Rodrigues PR, Pulido DC, Burkhardt RN, Panda O, Zhang YK, Gudibanda P, Ruvinsky I, *et al.* 2019. An excreted small molecule promotes *C. elegans* reproductive development and aging. Nat Chem Biol. 15(8):838–845. doi:10.1038/s41589-019-0321-7.

Ludewig AH, Gimond C, Judkins JC, Thornton S, Pulido DC, Micikas RJ, Döring F, Antebi A, Braendle C, Schroeder FC. 2017. Larval crowding accelerates *C. elegans* development and reduces lifespan. PLoS Genet. 13(4):e1006717. doi:10.1371/journal.pgen.1006717.

Ludewig AH, Schroeder FC. 2013. Ascaroside signaling in *C. elegans*. WormBook. 1–22. doi:10.1895/wormbook.1.155.1.

Luo S, Murphy CT. 2011. *Caenorhabditis elegans* reproductive aging: regulation and underlying mechanisms. Genesis. 49(2):53–65. doi:10.1002/dvg.20694.

Lynch M, Walsh B. 1998. Genetics and analysis of quantitative traits. Sinauer Associates.

Mack HID, Heimbucher T, Murphy CT. 2018. The nematode *Caenorhabditis elegans* as a model for aging research. Drug Discov Today Dis Models. 27:3–13. doi:10.1016/j.ddmod.2018.11.001.

Mackay TFC, Stone EA, Ayroles JF. 2009. The genetics of quantitative traits: challenges and prospects. Nat Rev Genet. 10(8):565–577. doi:10.1038/nrg2612.

MacNeil LT, Watson E, Arda HE, Zhu LJ, Walhout AJM. 2013. Diet-induced developmental acceleration independent of TOR and insulin in *C. elegans*. Cell. 153:240–252. doi:10.1016/j.cell.2013.02.049.

Maier W, Adilov B, Regenass M, Alcedo J. 2010. A neuromedin U receptor acts with the sensory system to modulate food type-dependent effects on *C. elegans* lifespan. PLoS Biol. 8(5):804–809. doi:10.1371/journal.pbio.1000376.

Maklakov AA, Carlsson H, Denbaum P, Lind MI, Mautz B, Hinas A, Immler S. 2017. Antagonistically pleiotropic allele increases lifespan and late-life reproduction at the cost of early-life reproduction and individual fitness. Proc R Soc Lond B Biol Sci. 284(1856):20170376. doi:10.1098/rspb.2017.0376.

Malone CJ, Misner L, Le Bot N, Tsai M-C, Campbell JM, Ahringer J, White JG. 2003. The *C. elegans* hook protein, ZYG-12, mediates the essential attachment between the centrosome and nucleus. Cell. 115(7):825–836. doi:10.1016/S0092-8674(03)00985-1.

Masri L, Schulte RD, Timmermeyer N, Thanisch S, Crummenerl LL, Jansen G, Michiels NK, Schulenburg H. 2013. Sex differences in host defence interfere with parasite-mediated selection for outcrossing during host-parasite coevolution. Ecol Lett. 16(4):461–468. doi:10.1111/ele.12068.

Mata-Cabana A, Pérez-Nieto C, Olmedo M. 2021. Nutritional control of postembryonic development progression and arrest in *Caenorhabditis elegans*. Adv Genet. 107:33–87. doi:10.1016/bs.adgen.2020.11.002.

Maulana MI, Riksen JAG, Snoek BL, Kammenga JE, Sterken MG. 2022. The genetic architecture underlying body-size traits plasticity over different temperatures and developmental stages in *Caenorhabditis elegans*. Heredity (Edinb). 128(5):313–324. doi:10.1038/s41437-022-00528-y.

Maupas E. 1899. La mue et l'enkystement chez les nématodes. Arch Zool Exp Gen. 7:563–628.

Maupas E. 1900. Modes et formes de reproduction des nématodes. Arch Zool Exp. 8:463–624.

Mayr E. 1963. Animal species and evolution. Harvard University Press.

McGrath PT, Rockman MV, Zimmer M, Jang H, Macosko EZ, Kruglyak L, Bargmann CI. 2009. Quantitative mapping of a digenic behavioral trait implicates globin variation in *C. elegans* sensory behaviors. Neuron. 61(5):692–699. doi:10.1016/j.neuron.2009.02.012.

McGrath PT, Xu Y, Ailion M, Garrison JL, Butcher RA, Bargmann CI. 2011. Parallel evolution of domesticated Caenorhabditis species targets pheromone receptor genes. Nature. 477(7364):321–325. doi:10.1038/nature10378.

Medawar PB. 1952. An Unsolved Problem of Biology: An Inaugural Lecture Delivered at University College, London, 6 December, 1951. H.K. Lewis and Company.

Mendenhall AR, Wu D, Park S-K, Cypser JR, Tedesco PM, Link Christopher D, Phillips Patrick C, Johnson TE. 2011. Genetic dissection of late-life fertility in *Caenorhabditis elegans*. J Gerontol A Biol Sci Med Sci. 66(8):842–854. doi:10.1093/gerona/glr089.

Metzger BPH, Wittkopp PJ. 2019. Compensatory trans-regulatory alleles minimizing variation in TDH3 expression are common within *Saccharomyces cerevisiae*. Evol Lett. 3(5):448–461. doi:10.1002/evl3.137.

Mignerot L, Gimond C, Bolelli L, Bouleau C, Sandjak A, Boulin T, Braendle C. 2024. Natural variation in the *Caenorhabditis elegans* egg-laying circuit modulates an intergenerational fitness tradeoff. Elife. 12:RP88253. doi:10.7554/eLife.88253.

Mishra S, Dabaja M, Akhlaq A, Pereira B, Marbach K, Rovcanin M, Chandra R, Caballero A, Fernandes de Abreu D, Ch'ng Q, *et al.* 2023. Specific sensory neurons and insulin-like peptides modulate food type-dependent oogenesis and fertilization in *Caenorhabditis elegans*. Elife. 12:e83224. doi:10.7554/eLife.83224.

Moran NA. 1992. The evolutionary maintenance of alternative phenotypes. Am Nat. 139(5):971–989. doi:10.1086/285369.

Morran LT, Cappy BJ, Anderson JL, Phillips PC. 2009. Sexual partners for the stressed: facultative outcrossing in the self-fertilizing nematode *Caenorhabditis elegans*. Evolution. 63(6):1473–1482. doi:10.1111/j.1558-5646.2009.00652.x.

Morris JZ, Tissenbaum HA, Ruvkun G. 1996. A phosphatidylinositol-3-OH kinase family member regulating longevity and diapause in *Caenorhabditis elegans*. Nature. 382(6591):536–539. doi:10.1038/382536a0.

Motola DL, Cummins CL, Rottiers V, Sharma KK, Li T, Li Y, Suino-Powell K, Xu HE, Auchus RJ, Antebi A, *et al.* 2006. Identification of ligands for DAF-12 that govern dauer formation and reproduction in *C. elegans*. Cell. 124(6):1209–1223. doi:10.1016/j.cell.2006.01.037.

Mouchiroud L, Houtkooper RH, Moullan N, Katsyuba E, Ryu D, Cantó C, Mottis A, Jo Y-S, Viswanathan M, Schoonjans K, *et al.* 2013. The NAD(+)/sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling. Cell. 154(2):430–441. doi:10.1016/j.cell.2013.06.016.

Munday PL, Buston PM, Warner RR. 2006. Diversity and flexibility of sex-change strategies in animals. Trends Ecol Evol. 21(2):89–95. doi:10.1016/j.tree.2005.10.020.

Murray RL, Cutter AD. 2011. Experimental evolution of sperm count in protandrous self-fertilizing hermaphrodites. J Exp Biol. 214(Pt 10):1740–1747. doi:10.1242/jeb.053181.

Muschiol D, Schroeder F, Traunspurger W. 2009. Life cycle and population growth rate of *Caenorhabditis elegans* studied by a new method. BMC Ecol. 9:14. doi:10.1186/1472-6785-9-14.

Nance J, Frøkjær-Jensen C. 2019. The *Caenorhabditis elegans* transgenic toolbox. Genetics. 212(4):959–990. doi:10.1534/genetics.119.301506.

Neal SJ, Takeishi A, O'Donnell MP, Park J, Hong M, Butcher RA, Kim K, Sengupta P. 2015. Feeding state-dependent regulation of developmental plasticity via CaMKI and neuroendocrine signaling. Elife. 4:e10110. doi:10.7554/eLife.10110.

Nigon VM, Félix M-A. 2017. History of research on *C. elegans* and other free-living nematodes as model organisms. WormBook. 2017:1–84. doi:10.1895/wormbook.1.181.1.

Nijhout HF. 2003. Development and evolution of adaptive polyphenisms. Evol Dev. 5(1):9–18. doi:10.1046/j.1525-142X.2003.03003.x.

Noble LM, Chang AS, McNelis D, Kramer M, Yen M, Nicodemus JP, Riccardi DD, Ammerman P, Phillips M, Islam T, *et al.* 2015. Natural variation in plep-1 causes male-male copulatory behavior in *C. elegans*. Curr Biol. 25(20):2730–2737. doi:10.1016/j.cub.2015.09.019.

Noble LM, Chelo I, Guzella T, Afonso B, Riccardi DD, Ammerman P, Dayarian A, Carvalho S, Crist A, Pino-Querido A, *et al.* 2017. Polygenicity and epistasis underlie fitness-proximal traits in the *Caenorhabditis elegans* multiparental experimental evolution (CeMEE) panel. Genetics. 207(4):1663–1685. doi:10.1534/genetics.117.300406.

Noble LM, Rockman MV, Teotónio H. 2021. Gene-level quantitative trait mapping in *Caenorhabditis elegans*. G3 (Bethesda). 11(2):jkaa061. doi:10.1093/g3journal/jkaa061.

Noble LM, Yuen J, Stevens L, Moya N, Persaud R, Moscatelli M, Jackson JL, Zhang G, Chitrakar R, Baugh LR, *et al.* 2021. Selfing is the safest sex for *Caenorhabditis tropicalis*. eLife. 10:e62587. doi:10.7554/eLife.62587.

O'Donnell MP, Chao P-H, Kammenga JE, Sengupta P. 2018. Rictor/TORC2 mediates gut-to-brain signaling in the regulation of phenotypic plasticity in *C. elegans*. PLoS Genet. 14(2):e1007213. doi:10.1371/journal.pgen.1007213.

Ogawa A, Streit A, Antebi A, Sommer RJ. 2009. A conserved endocrine mechanism controls the formation of dauer and infective larvae in nematodes. Curr Biol. 19(1):67–71. doi:10.1016/j.cub.2008.11.063.

Oh SW, Mukhopadhyay A, Svrzikapa N, Jiang F, Davis RJ, Tissenbaum HA. 2005. JNK regulates lifespan in *Caenorhabditis elegans* by modulating nuclear translocation of forkhead transcription factor/DAF-16. Proc Natl Acad Sci U S A. 102(12):4494–4499. doi:10.1073/pnas.0500749102.

Okumura E, Tanaka R, Yoshiga T. 2013. Species-specific recognition of the carrier insect by dauer larvae of the nematode *Caenorhabditis japonica*. J Exp Biol. 216(Pt 4):568–572. doi:10.1242/jeb.073593.

Osche G. 1956. Die Präadaptation freilebender Nematoden an den Parasitismus. Zool Anz. 19:391–396.

Ostrow D, Phillips N, Avalos A, Blanton D, Boggs A, Keller T, Levy L, Rosenbloom J, Baer CF. 2007. Mutational bias for body size in rhabditid nematodes. Genetics. 176(3):1653–1661. doi:10.1534/genetics.107.074666.

Ow MC, Borziak K, Nichitean AM, Dorus S, Hall SE. 2018. Early experiences mediate distinct adult gene expression and reproductive programs in *Caenorhabditis elegans*. PLoS Genet. 14(2):e1007219. doi:10.1371/journal.pgen.1007219.

Ow MC, Nichitean AM, Hall SE. 2021. Somatic aging pathways regulate reproductive plasticity in *Caenorhabditis elegans*. Elife. 10:e61459. doi:10.7554/eLife.61459.

Paaby AB, Blacket MJ, Hoffmann AA, Schmidt PS. 2010. Identification of a candidate adaptive polymorphism for Drosophila life history by parallel independent clines on two continents. Mol Ecol. 19(4):760–774. doi:10.1111/j.1365-294X.2009.04508.x.

Paaby AB, Schmidt PS. 2008. Functional significance of allelic variation at methuselah, an aging gene in Drosophila. PLoS One. 3(4):e1987. doi:10.1371/journal.pone.0001987.

Paaby AB, Schmidt PS. 2009. Dissecting the genetics of longevity in *Drosophila melanogaster*. Fly (Austin). 3(1):29–38. doi:10.4161/fly.3.1.7771.

Palopoli MF, Rockman MV, Tinmaung A, Ramsay C, Curwen S, Aduna A, Laurita J, Kruglyak L. 2008. Molecular basis of the copulatory plug polymorphism in *Caenorhabditis elegans*. Nature. 454(7207): 1019–1022. doi:10.1038/nature07171.

Pannell JR. 2002. The evolution and maintenance of androdioecy. Annu Rev Ecol Syst. 33:397–425. doi:10.1146/annurev.ecolsys.33.010802.150419.

Park JY, Joo HJ, Park S, Paik YK. 2019. Ascaroside pheromones: chemical biology and pleiotropic neuronal functions. Int J Mol Sci. 20(16):3898. doi:10.3390/ijms20163898.

Partridge L, Gems D, Withers DJ. 2005. Sex and death: what is the connection? Cell. 120(4):461–472. doi:10.1016/j.cell.2005.01.026.

Patel MN, Knight CG, Karageorgi C, Leroi AM. 2002. Evolution of germ-line signals that regulate growth and aging in nematodes. Proc Natl Acad Sci U S A. 99(2):769–774. doi:10.1073/pnas.012511099.

Pekar O, Ow MC, Hui KY, Noyes MB, Hall SE, Hubbard EJA. 2017. Linking the environment, DAF-7/TGFβ signaling and LAG-2/DSL ligand expression in the germline stem cell niche. Development. 144(16):2896–2906. doi:10.1242/dev.147660.

Perez MF, Francesconi M, Hidalgo-Carcedo C, Lehner B. 2017. Maternal age generates phenotypic variation in *Caenorhabditis elegans*. Nature. 552(7683):106–109. doi:10.1038/nature25012.

Perez MF, Lehner B. 2019. Intergenerational and transgenerational epigenetic inheritance in animals. Nat Cell Biol. 21(2):143–151. doi:10.1038/s41556-018-0242-9

Perez MF, Shamalnasab M, Mata-Cabana A, Della Valle S, Olmedo M, Francesconi M, Lehner B. 2021. Neuronal perception of the social environment generates an inherited memory that controls the development and generation time of *C. elegans*. Curr Biol. 31(19): 4256–4268.e7. doi:10.1016/j.cub.2021.07.031.

Peters AD, Halligan DL, Whitlock MC, Keightley PD. 2003. Dominance and overdominance of mildly deleterious induced mutations for fitness traits in *Caenorhabditis elegans*. Genetics. 165(2):589–599. doi:10.1093/genetics/165.2.589.

Peters AD, Keightley PD. 2000. A test for epistasis among induced mutations in *Caenorhabditis elegans*. Genetics. 156(4):1635–1647. doi:10.1093/genetics/156.4.1635.

Petersen C, Saebelfeld M, Barbosa C, Pees B, Hermann RJ, Schalkowski R, Strathmann EA, Dirksen P, Schulenburg H. 2015. Ten years of life in compost: temporal and spatial variation of North German *Caenorhabditis eleganspopulations*. Ecol Evol. 5(16): 3250–3263. doi:10.1002/ece3.1605.

Petrella LN. 2014. Natural variants of *C. elegans* demonstrate defects in both sperm function and oogenesis at elevated temperatures. PLoS One. 9(11):e112377. doi:10.1371/journal.pone.0112377.

Phillips PC. 2008. Epistasis–the essential role of gene interactions in the structure and evolution of genetic systems. Nat Rev Genet. 9(11):855–867. doi:10.1038/nrg2452.

Pires-daSilva A. 2007. Evolution of the control of sexual identity in nematodes. Semin Cell Dev Biol. 18(3):362–370. doi:10.1016/j.semcdb.2006.11.014.

Pollard DA, Rockman MV. 2013. Resistance to germline RNA interference in a *Caenorhabditis elegans* wild isolate exhibits complexity and nonadditivity. G3 (Bethesda). 3(6):941–947. doi:10.1534/g3.113.005785

Porazinska DL, Giblin-Davis RM, Faller L, Farmerie W, Kanzaki N, Morris K, Powers TO, Tucker AE, Sung W, Thomas WK. 2009. Evaluating high-throughput sequencing as a method for metagenomic analysis of nematode diversity. Mol Ecol Resour. 9(6): 1439–1450. doi:10.1111/j.1755-0998.2009.02611.x.

Poullet N, Vielle A, Gimond C, Ferrari C, Braendle C. 2015. Evolutionarily divergent thermal sensitivity of germline development and fertility in hermaphroditic *Caenorhabditis nematodes*. Evol Dev. 17(6):380–397. doi:10.1111/ede.12170.

Powell JR. 1997. Progress and prospects in evolutionary biology: the drosophila model. Oxford University Press.

Prasad NG, Joshi A. 2003. What have two decades of laboratory life-history evolution studies on *Drosophila melanogaster* taught us? J Genet. 82(1–2):45–76. doi:10.1007/BF02715881.

Price TD, Qvarnström A, Irwin DE. 2003. The role of phenotypic plasticity in driving genetic evolution. Proc Biol Sci. 270(1523): 1433–1440. doi:10.1098/rspb.2003.2372.

Price T, Schluter D. 1991. On the low heritability of life-history traits. Evolution. 45:853–861. doi:10.2307/2409693.

Proulx SR, Dey S, Guzella T, Teotónio H. 2019. How differing modes of non-genetic inheritance affect population viability in fluctuating environments. Ecol Lett. 22(11):1767–1775. doi:10.1111/ele.13355.

Proulx SR, Teotónio H. 2017. What kind of maternal effects can be selected for in fluctuating environments? Am Nat. 189(6): E118–E137. doi:10.1086/691423.

Rashid S, Wong C, Roy R. 2021. Developmental plasticity and the response to nutrient stress in *Caenorhabditis elegans*. Dev Biol. 475: 265–276. doi:10.1016/j.ydbio.2021.01.015.

Richaud A, Zhang G, Lee D, Lee J, Félix M-A. 2018. The local coexistence pattern of selfing genotypes in *Caenorhabditis elegans* natural metapopulations. Genetics. 208(2):807–821. doi:10.1534/genetics.117.300564.

Riska B. 1989. Composite traits, selection response, and evolution. Evolution. 43:1172–1191. doi:10.2307/2409355.

Rockman MV. 2012. The QTN program and the alleles that matter for evolution: all that's gold does not glitter. Evolution. 66(1):1–17. doi:10.1111/j.1558-5646.2011.01486.x.

Rockman MV, Kruglyak L. 2009. Recombinational landscape and population genomics of *Caenorhabditis elegans*. PLoS Genet. 5(3): e1000419. doi:10.1371/journal.pgen.1000419.

Rockman MV, Skrovanek SS, Kruglyak L. 2010. Selection at linked sites shapes heritable phenotypic variation in *C. elegans*. Science. 330(6002):372–376. doi:10.1126/science.1194208.

Rodriguez M, Snoek LB, Riksen JAG, Bevers RP, Kammenga JE. 2012. Genetic variation for stress-response hormesis in *C. elegans* lifespan. Exp Gerontol. 47(8):581–587. doi:10.1016/j.exger.2012.05.005.

Roff DA. 1992. The Evolution of Life Histories. New York (NY): Chapman and Hall.

Roff DA. 2007. Contributions of genomics to life-history theory. Nat Rev Genet. 8(2):116–125. doi:10.1038/nrg2040.

Roff DA, Fairbairn DJ. 2007. The evolution of trade-offs: where are we? J Evol Biol. 20(2):433–447. doi:10.1111/j.1420-9101.2006.01255.x.

Rose MR, Bradley TJ. 1998. Evolutionary physiology of the cost of reproduction. Oikos. 83(3):443. doi:10.2307/3546672.

Rose MR, Vu LN, Park SU, Graves Jr JL. 1992. Selection on stress resistance increases longevity in *Drosophila melanogaster*. Exp Gerontol. 27(2):241–250. doi:10.1016/0531-5565(92)90048-5.

Salomon MP, Ostrow D, Phillips N, Blanton D, Bour W, Keller TE, Levy L, Sylvestre T, Upadhyay A, Baer CF. 2009. Comparing mutational and standing genetic variability for fitness and size in *Caenorhabditis briggsae* and *C. elegans*. Genetics. 183(2):685–692. doi:10.1534/genetics.109.107383.

Samuel BS, Rowedder H, Braendle C, Félix M-A, Ruvkun G. 2016. *Caenorhabditis elegans* responses to bacteria from its natural habitats. Proc Natl Acad Sci U S A. 113(27):E3941–E3949. doi:10.1073/pnas.1607183113.

Savory FR, Benton TG, Varma V, Hope IA, Sait SM. 2014. Stressful environments can indirectly select for increased longevity. Ecol Evol. 4(7):1176–1185. doi:10.1002/ece3.1013.

Schaedel ON, Gerisch B, Antebi A, Sternberg PW. 2012. Hormonal signal amplification mediates environmental conditions during development and controls an irreversible commitment to adulthood. PLoS Biol. 10(4):e1001306. doi:10.1371/journal.pbio.1001306.

Schafer WR. 2005. Egg-laying. WormBook. doi:10.1895/wormbook.1.38.1.

Schärer L. 2009. Tests of sex allocation theory in simultaneously hermaphroditic animals. Evolution. 63(6):1377–1405. doi:10.1111/j.1558-5646.2009.00669.x.

Scharf A, Pohl F, Egan BM, Kocsisova Z, Kornfeld K. 2021. Reproductive aging in *Caenorhabditis elegans*: from molecules to ecology. Front Cell Dev Biol. 9:718522. doi:10.3389/fcell.2021.718522.

Schedl T, Kimble J. 1988. fog-2, a germ-line-specific sex determination gene required for hermaphrodite spermatogenesis in *Caenorhabditis elegans*. Genetics. 119(1):43–61. doi:10.1093/genetics/119.1.43.

Schiffer PH, Danchin EGJ, Burnell AM, Creevey CJ, Wong S, Dix I, O'Mahony G, Culleton BA, Rancurel C, Stier G, *et al.* 2019. Signatures of the evolution of parthenogenesis and cryptobiosis in the genomes of panagrolaimid nematodes. iScience. 21:587–602. doi:10.1016/j.isci.2019.10.039.

Schindler AJ, Baugh LR, Sherwood DR. 2014. Identification of late larval stage developmental checkpoints in *Caenorhabditis elegans* regulated by insulin/IGF and steroid hormone signaling pathways. PLoS Genet. 10(6):e1004426. doi:10.1371/journal.pgen.1004426.

Schmidt PS, Paaby AB, Heschel MS. 2005. Genetic variance for diapause expression and associated life histories in *Drosophila melanogaster*. Evolution. 59(12):2616–2625.

Schoech AP, Weissbrod O, O'Connor LJ, Patterson N, Shi H, Reshef Y, Price AL. 2020. Negative short-range genomic autocorrelation of causal effects on human complex traits. bioRxiv 2020.09.23.310748. https://doi.org/10.1101/2020.09. 23.310748, preprint: not peer reviewed.

Schulenburg H, Félix M-A. 2017. The natural biotic environment of *Caenorhabditis elegans*. Genetics. 206(1):55–86. doi:10.1534/genetics.116.195511.

Seidel HS, Kimble J. 2011. The oogenic germline starvation response in *C. elegans*. PLoS One. 6(12):e28074. doi:10.1371/journal.pone.0028074.

Shaw WM, Luo S, Landis J, Ashraf J, Murphy CT. 2007. The *C. elegans* TGF-beta dauer pathway regulates longevity via insulin signaling. Curr Biol. 17(19):1635–1645. doi:10.1016/j.cub.2007.08.058.

Shook DR, Brooks A, Johnson TE. 1996. Mapping quantitative trait loci affecting life history traits in the nematode *Caenorhabditis elegans*. Genetics. 142(3):801–817. doi:10.1093/genetics/142.3.801.

Shook DR, Johnson TE. 1999. Quantitative trait loci affecting survival and fertility-related traits in *Caenorhabditis elegans* show genotype-environment interactions, pleiotropy and epistasis. Genetics. 153(3):1233–1243. doi:10.1093/genetics/153.3.1233.

Singson A. 2001. Every sperm is sacred: fertilization in *Caenorhabditis elegans*. Dev Biol. 230(2):101–109. doi:10.1006/dbio.2000.0118.

Sloat SA, Noble LM, Paaby AB, Bernstein M, Chang A, Kaur T, Yuen J, Tintori SC, Jackson JL, Martel A, *et al.* 2022. Caenorhabditis nematodes colonize ephemeral resource patches in neotropical forests. Ecol Evol. 12(7):e9124. doi:10.1002/ece3.9124.

Sloat S, Rockman M. 2023. Sexual antagonism evolves when autosomes influence offspring sex ratio. bioRxiv 2023.06.14.544982. https://doi.org/10.1101/2023.06.14.544982, preprint: not peer reviewed

Sommer RJ. 2015. Pristionchus pacificus: a nematode model for comparative and evolutionary biology. Brill.

Sommer RJ, Ogawa A. 2011. Hormone signaling and phenotypic plasticity in nematode development and evolution. Curr Biol. 21(18):R758–R766. doi:10.1016/j.cub.2011.06.034.

Sowa JN, Mutlu AS, Xia F, Wang MC. 2015. Olfaction modulates reproductive plasticity through neuroendocrine signaling in *Caenorhabditis elegans*. Curr Biol. 25(17):2284–2289. doi:10.1016/j.cub.2015.07.023.

Stastna JJ, Snoek LB, Kammenga JE, Harvey SC. 2015. Genotype-dependent lifespan effects in peptone deprived *Caenorhabditis elegans*. Sci Rep. 5:16259. doi:10.1038/srep16259.

Stearns SC. 1989. Trade-offs in life-history evolution. Funct Ecol. 3:259–268. doi:10.2307/2389364.

Stearns SC. 1992. The Evolution of Life Histories. Oxford (UK): Oxford University Press.

Stearns SC. 2000. Life history evolution: successes, limitations, and prospects. Naturwissenschaften.87(11):476–486. doi:10.1007/s001140050763.

Stebbins GL. 1957. Self fertilization and population variability in the higher plants. Am Nat. 91:337–354. doi:10.1086/281999.

Sterken MG, Bevers RPJ, Volkers RJM, Riksen JAG, Kammenga JE, Snoek BL. 2020. Dissecting the eQTL micro-architecture in *Caenorhabditis elegans*. Front Genet. 11:501376. doi:10.3389/fgene.2020.501376.

Sterken MG, Snoek LB, Kammenga JE, Andersen EC. 2015. The laboratory domestication of *Caenorhabditis elegans*. Trends Genet. 31(5):224–231. doi:10.1016/j.tig.2015.02.009

Stevens L, Félix M-A, Beltran T, Braendle C, Caurcel C, Fausett S, Fitch D, Frézal L, Gosse C, Kaur T, *et al.* 2019. Comparative genomics of 10 new Caenorhabditis species. Evol Lett. 3(2):217–236. doi:10.1002/evl3.110.

Stevens L, Rooke S, Falzon LC, Machuka EM, Momanyi K, Murungi MK, Njoroge SM, Odinga CO, Ogendo A, Ogola J, *et al.* 2020. The genome of *Caenorhabditis bovis*. Curr Biol. 30(6):1023–1031.e4. doi:10.1016/j.cub.2020.01.074

Stojanovski K, Gheorghe I, Lenart P, Lanjuin A, Mair WB, Towbin BD. 2023. Maintenance of appropriate size scaling of the *C. elegans* pharynx by YAP-1. Nat Commun. 14(1):7564. doi:10.1038/s41467-023-43230-1.

Streit A. 2008. Reproduction in Strongyloides (Nematoda): a life between sex and parthenogenesis. Parasitology. 135(3):285–294. doi:10.1017/S003118200700399X.

Sudhaus W. 1976. Vergleichende Untersuchungen zur Phylogenie, Systematik, Ökologie, Biologie und Ethologie der Rhabditidae (Nematoda). Zoologica. 43:1–229.

Sudhaus W. 2010. Preadaptive plateau in Rhabditida (Nematoda) allowed the repeated evolution of zooparasites, with an outlook on evolution of life cycles within Spiroascarida. Palaeodiversity. 3 (Supplement):117–130.

Sudhaus W, Kiontke K. 2007. Comparison of the cryptic nematode species *Caenorhabditis brenneri* sp. n. and C. Remanei (Nematoda: Rhabditidae) with the stem species pattern of the *Caenorhabditis elegans* group. Zootaxa. 1456:45–62. doi:10.11646/zootaxa.1456.1.2.

Sulston JE, Horvitz HR. 1977. Post-embryonic cell lineages of the nematode, *Caenorhabditis elegans*. Dev Biol. 56(1):110–156. doi:10.1016/0012-1606(77)90158-0.

Sun S, Kanzaki N, Dayi M, Maeda Y, Yoshida A, Tanaka R, Kikuchi T. 2022. The compact genome of *Caenorhabditis niphades* n. sp., isolated from a wood-boring weevil, *Niphades variegatus*. BMC Genomics. 23(1):765. doi:10.1186/s12864-022-09011-8

Tanaka R, Okumura E, Yoshiga T. 2010. Survivorship of *Caenorhabditis japonica* dauer larvae naturally associated with the shield bug. *Parastrachia japonensis*. Nematol Res. 40:. doi:10.3725/jjn.40.47.

Tandonnet S, Farrell MC, Koutsovoulos GD, Blaxter ML, Parihar M, Sadler PL, Shakes DC, Pires-daSilva A. 2018. Sex- and gamete-specific patterns of X chromosome segregation in a trioecious nematode. Curr Biol. 28(1):93–99.e3. doi:10.1016/j.cub.2017.11.037.

Tatar M. 2023. Stalking the link between reproduction and aging: after decades of research, it still remains a mystery whether and how reproduction drives the process of aging: after decades of research, it still remains a mystery whether and how reproduction drives the process of aging. EMBO Rep. 24(6):e57374. doi:10.15252/embr.202357374

Teotonio H, Carvalho S, Manoel D, Roque M, Chelo IM. 2012. Evolution of outcrossing in experimental populations of *Caenorhabditis elegans*. PLoS One. 7(4):e35811. doi:10.1371/journal.pone.0035811.

Teotónio H, Estes S, Phillips PC, Baer CF. 2017. Experimental evolution with Caenorhabditis nematodes. Genetics. 206(2):691–716. doi:10.1534/genetics.115.186288.

Teotónio H, Manoel D, Phillips PC. 2006. Genetic variation for outcrossing among *Caenorhabditis elegans* isolates. Evolution. 60(6):1300–1305.

Teterina AA, Willis JH, Lukac M, Jovelin R, Cutter AD, Phillips PC. 2023. Genomic diversity landscapes in outcrossing and selfing Caenorhabditis nematodes. PLoS Genet. 19(7):e1010879. doi:10.1371/journal.pgen.1010879.

Theologidis I, Chelo IM, Goy C, Teotónio H. 2014. Reproductive assurance drives transitions to self-fertilization in experimental *Caenorhabditis elegans*. BMC Biol. 12:93. doi:10.1186/s12915-014-0093-1.

Thomas CG, Wang W, Jovelin R, Ghosh R, Lomasko T, Trinh Q, Kruglyak L, Stein LD, Cutter AD. 2015. Full-genome evolutionary histories of selfing, splitting, and selection in Caenorhabditis. Genome Res. 25(5):667–678. doi:10.1101/gr.187237.114.

Thomas CG, Woodruff GC, Haag ES. 2012. Causes and consequences of the evolution of reproductive mode in Caenorhabditis nematodes. Trends Genet. 28(5):213–220. doi:10.1016/j.tig.2012.02.007

Tissenbaum HA, Guarente L. 2001. Increased dosage of a sir-2 gene extends lifespan in *Caenorhabditis elegans*. Nature. 410(6825):227–230. doi:10.1038/35065638.

Travisano M, Shaw RG. 2012. Lost in the map. Evolution. 67(2):305–314. doi:10.1111/j.1558-5646.2012.01802.x.

Trent C. 1982. Genetic and behavioral studies of the egg-laying system of *Caenorhabditis elegans*. Science. 216(4549):1012–1014. doi:10.1126/science.6805073.

Uno M, Nishida E. 2016. Lifespan-regulating genes in *C. elegans*. NPJ Aging Mech Dis. 2:16010. doi:10.1038/npjamd.2016.10.

Uppaluri S, Weber SC, Brangwynne CP. 2016. Hierarchical size scaling during multicellular growth and development. Cell Rep. 17(2):345–352. doi:10.1016/j.celrep.2016.09.007.

Vadnal J, Ratnappan R, Keaney M, Kenney E, Eleftherianos I, O'Halloran D, Hawdon JM. 2017. Identification of candidate infection genes from the model entomopathogenic nematode *Heterorhabditis bacteriophora*. BMC Genomics. 18(1):8. doi:10.1186/s12864-016-3468-6.

Van Goor J, Shakes DC, Haag ES. 2021. Fisher vs. the worms: extraordinary sex ratios in nematodes and the mechanisms that produce them. Cells. 10(7):1793. doi:10.3390/cells10071793.

Vassilieva LL, Hook AM, Lynch M. 2000. The fitness effects of spontaneous mutations in *Caenorhabditis elegans*. Evolution. 54(4):1234–1246. doi:10.1111/j.0014-3820.2000.tb00557.x.

Vassilieva LL, Lynch M. 1999. The rate of spontaneous mutation for life-history traits in *Caenorhabditis elegans*. Genetics. 151(1):119–129. doi:10.1093/genetics/151.1.119.

Vellai T, Takacs-Vellai K, Zhang Y, Kovacs AL, Orosz L, Müller F. 2003. Genetics: influence of TOR kinase on lifespan in *C. elegans*. Nature. 426(6967):620. doi:10.1038/426620a.

Via S, Lande R. 1985. Genotype-environment interaction and the evolution of phenotypic plasticity. Evolution. 39:505–522. doi:10.2307/2408649.

Via S, Lande R. 1987. Evolution of genetic variability in a spatially heterogeneous environment: effects of genotype-environment interaction. Genet Res. 49:147–156. doi:10.1017/S001667230002694X.

Vigne P, Gimond C, Ferrari C, Vielle A, Hallin J, Pino-Querido A, El Mouridi S, Mignerot L, Frøkjær-Jensen C, Boulin T, *et al.* 2021. A single-nucleotide change underlies the genetic assimilation of a plastic trait. Sci Adv. 7(6):eabd9941. doi:10.1126/sciadv.abd9941.

Viney ME, Gardner MP, Jackson JA. 2003. Variation in *Caenorhabditis elegans* dauer larva formation. Dev Growth Differ. 45(4):389–396. doi:10.1046/j.1440-169X.2003.00703.x.

Virk B, Correia G, Dixon DP, Feyst I, Jia J, Oberleitner N, Briggs Z, Hodge E, Edwards R, Ward J, *et al.* 2012. Excessive folate synthesis limits lifespan in the *C. elegans*: *E. coli* aging model. BMC Biol. 10:67. doi:10.1186/1741-7007-10-67.

Vlaar LE, Bertran A, Rahimi M, Dong L, Kammenga JE, Helder J, Goverse A, Bouwmeester HJ. 2021. On the role of dauer in the adaptation of nematodes to a parasitic lifestyle. Parasit Vectors. 14(1):554. doi:10.1186/s13071-021-04953-6.

Walker DW, McColl G, Jenkins NL, Harris J, Lithgow GJ. 2000. Evolution of lifespan in *C. elegans*. Nature. 405(6784):296–297. doi:10.1038/35012693.

Walsh B, Lynch M. 2018. Evolution and selection of quantitative traits. Oxford University Press.

Wang Z, Zhou XE, Motola DL, Gao X, Suino-Powell K, Conneely A, Ogata C, Sharma KK, Auchus RJ, Lok JB, *et al.* 2009. Identification of the nuclear receptor DAF-12 as a therapeutic target in parasitic nematodes. Proc Natl Acad Sci U S A. 106(23):9138–9143. doi:10.1073/pnas.0904064106.

Ward S, Carrel JS. 1979. Fertilization and sperm competition in the nematode *Caenorhabditis elegans*. Dev Biol. 73(2):304–321. doi:10.1016/0012-1606(79)90069-1.

Watson E, MacNeil LT, Ritter AD, Yilmaz LS, Rosebrock AP, Caudy AA, Walhout AJM. 2014. Interspecies systems biology uncovers metabolites affecting *C. elegans* gene expression and life history traits. Cell. 156(4):759–770. doi:10.1016/j.cell.2014.01.047.

Weber KP, De S, Kozarewa I, Turner DJ, Babu MM, de Bono M. 2010. Whole genome sequencing highlights genetic changes associated with laboratory domestication of *C. elegans*. PLoS One. 5(11):e13922. doi:10.1371/journal.pone.0013922.

Webster AK, Chitrakar R, Taylor SM, Baugh LR. 2022. Alternative somatic and germline gene-regulatory strategies during starvation-induced developmental arrest. Cell Rep. 41(2):111473. doi:10.1016/j.celrep.2022.111473.

Webster AK, Jordan JM, Hibshman JD, Chitrakar R, Baugh LR. 2018. Transgenerational effects of extended dauer diapause on starvation survival and gene expression plasticity in *Caenorhabditis elegans*. Genetics. 210(1):263–274. doi:10.1534/genetics.118.301250

Weeks SC, Benvenuto C, Reed SK. 2006. When males and hermaphrodites coexist: a review of androdioecy in animals. Integr Comp Biol. 46(4):449–464. doi:10.1093/icb/icj048.

West-Eberhard MJ. 1986. Alternative adaptations, speciation, and phylogeny (A Review). Proc Natl Acad Sci U S A. 83(5):1388–1392. doi:10.1073/pnas.83.5.1388.

West-Eberhard MJ. 1989. Phenotypic plasticity and the origins of diversity. Annu Rev Ecol Syst. 20:249–278. doi:10.1146/annurev.es.20.110189.001341.

West-Eberhard MJ. 2003. Developmental plasticity and evolution. Oxford University Press.

Whiteman NK. 2022. Evolution in small steps and giant leaps. Evolution. 76(S1):67–77. doi:10.1111/evo.14432.

Widmayer SJ, Evans KS, Zdraljevic S, Andersen EC. 2022. Evaluating the power and limitations of genome-wide association studies in *Caenorhabditis elegans*. G3 (Bethesda). 12(7):jkac114. doi:10.1093/g3journal/jkac114

Williams GC. 1957. Pleiotropy, natural selection, and the evolution of senescence. Evolution. 11:398–411. doi:10.2307/2406060.

Williams GC. 1966. Natural selection, the costs of reproduction, and a refinement of Lack's principle. Am Nat. 100:687–690. doi:10.1086/282461.

Wong SS, Yu J, Schroeder FC, Kim DH. 2020. Population density modulates the duration of reproduction of *C. elegans*. Curr Biol. 30(13):2602–2607.e2. doi:10.1016/j.cub.2020.04.056.

Woodruff GC, Phillips PC. 2018. Field studies reveal a close relative of *C. elegans* thrives in the fresh figs of *Ficus septica* and disperses on its Ceratosolen pollinating wasps. BMC Ecol. 18(1):26. doi:10.1186/s12898-018-0182-z.

Xu W, Long L, Zhao Y, Stevens L, Felipe I, Munoz J, Ellis RE, McGrath PT. 2019. Evolution of Yin and Yang isoforms of a chromatin remodeling subunit precedes the creation of two genes. Elife. 8:e48119. doi:10.7554/eLife.48119.

Yamashita T, Ekino T, Kanzaki N, Shinya R. 2023. The developmental and structural uniqueness of the embryo of the extremophile viviparous nematode, *Tokorhabditis tufae*. Front Physiol. 14:1197477. doi:10.3389/fphys.2023.1197477.

Yengo L, Vedantam S, Marouli E, Sidorenko J, Bartell E, Sakaue S, Graff M, Eliasen AU, Jiang Y, Raghavan S, *et al.* 2022. A saturated map of common genetic variants associated with human height. Nature. 610(7933):704–712. doi:10.1038/s41586-022-05275-y.

Yoshiga T, Ishikawa Y, Tanaka R, Hironaka M, Okumura E. 2013. Species-specific and female host-biased ectophoresy in the roundworm *Caenorhabditis japonica*. Naturwissenschaften. 100(2):205–208. doi:10.1007/s00114-013-1011-z.

Zamanian M, Andersen EC. 2016. Prospects and challenges of CRISPR/Cas genome editing for the study and control of neglected vector-borne nematode diseases. FEBS J. 283(17):3204–3221. doi:10.1111/febs.13781.

Zhang F, Berg M, Dierking K, Félix M-A, Shapira M, Samuel BS, Schulenburg H. 2017. *Caenorhabditis elegans* as a model for microbiome research. Front Microbiol. 8:485. doi:10.3389/fmicb.2017.00485.

Zhang S, Li F, Zhou T, Wang G, Li Z. 2020. *Caenorhabditis elegans* as a useful model for studying aging mutations. Front Endocrinol (Lausanne). 11:554994. doi:10.3389/fendo.2020.554994.

Zhang G, Mostad JD, Andersen EC. 2021. Natural variation in fecundity is correlated with species-wide levels of divergence in *Caenorhabditis elegans*. G3 (Bethesda). 11(8):jkab168. doi:10.1093/g3journal/jkab168.

Zhang Y, Xu J, Puscau C, Kim Y, Wang X, Alam H, Hu PJ. 2008. *Caenorhabditis elegans* EAK-3 inhibits dauer arrest via nonautonomous regulation of nuclear DAF-16/FoxO activity. Dev Biol. 315(2):290–302. doi:10.1016/j.ydbio.2007.12.032.

Zhao Y, Long L, Wan J, Biliya S, Brady SC, Lee D, Ojemakinde A, Andersen EC, Vannberg FO, Lu H, *et al.* 2020. A spontaneous complex structural variant in rcan-1 increases exploratory behavior and laboratory fitness of *Caenorhabditis elegans*. PLoS Genet. 16(2):e1008606. doi:10.1371/journal.pgen.1008606.

Zhao Y, Long L, Xu W, Campbell RF, Large EE, Greene JS, McGrath PT. 2018. Changes to social feeding behaviors are not sufficient for fitness gains of the *Caenorhabditis elegans* N2 reference strain. Elife. 7:1921. doi:10.7554/eLife.38675.

Zhu Z, Han X, Wang Y, Liu W, Lu Y, Xu C, Wang X, Hao L, Song Y, Huang S, *et al.* 2019. Identification of specific nuclear genetic loci and genes that interact with the mitochondrial genome and contribute to fecundity in *Caenorhabditis elegans*. Front Genet. 10:28. doi:10.3389/fgene.2019.00028.

Zhu Z, Lu Q, Zeng F, Wang J, Huang S. 2015. Compatibility between mitochondrial and nuclear genomes correlates with the quantitative trait of lifespan in *Caenorhabditis elegans*. Sci Rep. 5:17303. doi:10.1038/srep17303.

Editor: A. Cutter