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Research Focus

One perfect worm

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Recent studies show that local populations of the nematode *Caenorhabditis elegans* possess nearly as much genetic variation as that seen in existing worldwide collections. This suggests either wide-ranging migration and intense natural selection or recent dispersal, perhaps by human association. Either way, the effective population size of this ubiquitous model organism is unexpectedly small.

The genetic history of *C. elegans*

Although Sydney Brenner is regarded as a clever geneticist, as far as we know the nematode *Caenorhabditis elegans* was not 'invented' in his laboratory during the 1960s. Nevertheless, despite an ongoing battle with *Drosophila melangoster* for the rights to the title of best genetically characterized metazoan, we know very little about the natural history of *C. elegans*. Studies of genetic variation among *C. elegans* natural isolates using microsattelites and single nucleotide polymorphisms (SNPs) have found that there is disturbingly little genetic variation within the entire species, despite its apparent worldwide distribution [1–4]. Why should individuals collected from Australia, America and the UK all have essentially identical genotypes? Overall, these isolates consist of single individuals isolated from nature and maintained as selfing lines. What has been sorely lacking is information regarding genetic variation within a local population of *C. elegans*. Such information is directly relevant to evolutionary questions, such as the role that males have in maintaining genetic variation, and is important for yielding insights into the function of specific genes, such as those involved in aging, within this important model system. Now, four recent studies have made comprehensive analyses of the levels of genetic variation within *C. elegans* natural populations [5–8].

Natural isolates

Using microsatellites, Haber *et al.* [6] have analyzed 23 new lines of *C. elegans* from northwest Germany, whereas Sivasundar and Hey [7] focused on 69 lines from the Los Angeles (USA) area. Barrière and Félix [5] collected > 1 000 individuals from several locations in France and extensively genotyped a subset of 55 using amplified fragment length polymorphisms (AFLPs). Cutter [8] analysed SNP variation in six genes in 118 strains, using many of the same lines as Barrière and Félix in addition to existing lines and a few lines from Scotland. Only a few lines have been analyzed because it has been difficult to isolate these small translucent worms from the sea of debris in which they are found. Sivasundar and Hey [7] have addressed this problem by using an clever RNA interference (RNAi) feeding treatment, which makes *C. elegans* 'dance' out of the dirt, while nematodes from other species remain still. Each of these studies has found ample genetic variation within these natural populations. Within their local French populations, Barrière and Félix found representatives of every known genotype that had previously been isolated from the worldwide collection. Each study also concluded that selfing is the predominant mode of reproduction within *C. elegans*, although they differ somewhat in their estimates of the prevalence of periodic outcrossing by males [9].

The major question that these studies raise, then, is how to reconcile the observation that single populations can possess nearly the same level of variation seen in within the species as a whole? Although, each group found some evidence for local population structure, generally, it seems that *C. elegans* is a widely distributed species with low levels of genetic variation, in which populations are similar to one another. What factors might drive this pattern?

Is there too much migration?

One possible explanation is that there are high levels of migration coupled with strong selection within natural populations [1]. *C. elegans* is primarily selfing, if there is 'one best way' of being a worm, then selection operating on the optimal genotype should constrain overall variation (particularly with genetic hitchhiking facilitated by selfing), with this pattern being propagated around the world through migration. High levels of migration over a long period alone cannot explain the similarity among natural isolates, because we would expect to see the accumulation of more neutral variation at locations such as introns and intergenic regions. Similarly, selection alone also cannot explain this pattern, because we would expect rapid differentiation among local populations at sites that are not under selection (selfing actually accelerates the differentiation process).

Indeed, Barrière and Félix found evidence for strong local differentiation that is not reflected in the worldwide distribution. So is there an 'über-worm' gallivanting around the world and displacing all others? Two lines of evidence argue against this. First, we know that there is significant mutational input at the level of nucleotide diversity [10], transcriptional regulation [11], morphology [12], life history [13] and behavior [14]; therefore, unique genetic variants should be continuously generated at

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Table 1. Comparison of genetic polymorphism between *C. elegans* and *C. remanei*

Gene	Function	Polymorphism in *C. elegans*	Polymorphism in *C. remanei*	Refs
odr-3	Neuronally expressed G-protein α-subunit	0.06×10^{-3}	12.9×10^{-3}	[2]
tra-2	Transmembrane receptor involved in sex determination	0	11.2×10^{-3}	[3]
glp-1	Transmembrane protein in the LIN-12/Notch family involved in germline proliferation	0.9×10^{-3}	18.8×10^{-3}	[3]
fem-3	Cytoplasmic protein that interacts with *tra-2* during sex determination	0	27.0×10^{-3}	[16]

different locations around the world. Selection would need to be truly overwhelming to counteract the variation expected to accumulate within local populations. A recent estimate that attempts to reconcile the rate of mutational input with the variation among populations suggests the worldwide effective population size of *C. elegans* to be 15 600 [15] – approximately the number of individuals found on a single crowded Petri dish in the laboratory. This number is consistent with estimates derived directly from the level of genetic variation within populations [1,5,8]. Second, a closely related nematode, *Caenorhabditis remanei*, has much more genetic diversity than existing natural isolates of *C. elegans* [2,3,16]. For example, a population of *C. remanei* collected from a single log in Ohio (USA) has as much genetic variation for chemosensory behavior as the entire worldwide distribution of *C. elegans*, while nucleotide diversity at specific genes can be as much as 180 times greater (Table 1) [2]. Similar results have been observed for genes involved in the sex determination pathway (Table 1) [3,16]. Interestingly, there is more variation within *C. elegans* at the mitochondrial locus, COII [3], perhaps because the much greater mutation rate in the mitochondrial genome leads to more rapid local differentiation [17]. However, the natural isolates of *C. elegans* are hardly devoid of variation, because there is differentiation at several sites in the genome [18], among developmental processes [19], in the frequency of males generated [20] and in behavioral traits [2,21], although absolute levels of variation overall tend to be low [2]. The level of polymorphism in *C. elegans* is similar to that of humans [5]. Differences in the mating system alone (selfing versus outcrossing) cannot explain this variation [22,3].

An obvious alternative hypothesis to explain the similarity among isolates despite substantial within-population variation is that most of these 'natural isolates' have recently been derived from a common source, spread around the globe and then accumulated some local variation [2]. Perhaps most telling in this regard is the high level of linkage disequilibrium found by Cutter [8]. It seems that markers spread across whole chromosomes are in strong linkage disequilibrium, as are markers across chromosomes (Figure 1). Humans are the likely culprits here, thus far most isolates have come from compost heaps and other similar human dominated environments. Thus, *C. elegans* might be a general human commensal that is spread by other invasive species such as snails [23] or by *C. elegans* researchers themselves, because some of the older isolates are genotypically similar to the standard laboratory strain. Regardless of how individual worms are being transported, the overall low levels of variation suggest that this movement around the world is pervasive and recent.

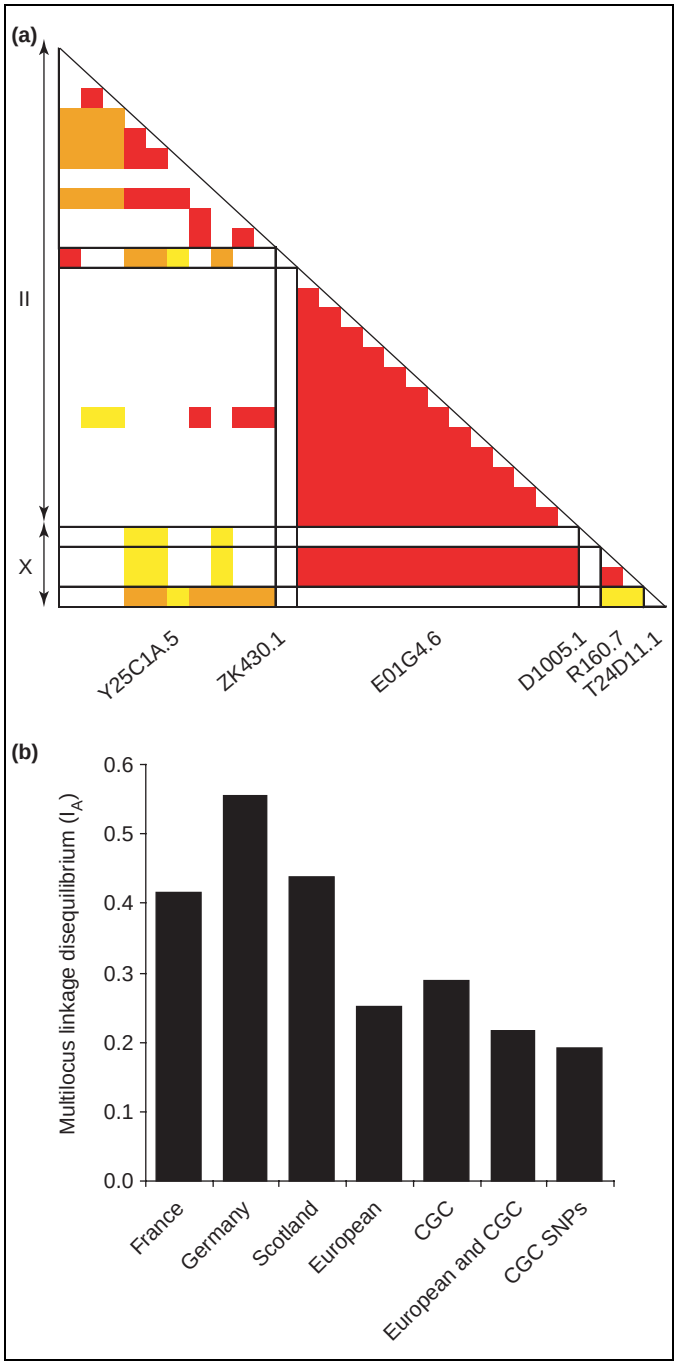

Figure 1. Patterns of linkage disequilibrium across the chromosome II and chromosome X in natural isolates of *C. elegans*. **(a)** Significant levels of linkage disequilibrium (red and yellow) exist both within and between chromosomes for European populations at six different loci. **(b)** Average levels of linkage disequilibria for various populations. 'CGC' refers to the older natural isolates from the *C. elegans* genetics center. Other estimates are based on the new collections discussed in the main text. The figure is reproduced, with permission, from Ref. [8] ©2006 Genetics Society of America.

Concluding remarks

If much of the natural diversity of *C. elegans* is dominated by human introduction, then they would join a long list of model organisms that thrive as human commensals, such as rats, mice, fruit flies and weeds (*Arabidopsis*). Nevertheless, true natural populations of *C. elegans* must exist somewhere. Cutter [8] suggests that existing levels of genetic diversity are consistent with a coalescence event sometime in the past 60 000 years. Perhaps these European populations, which are reminiscent of human African populations in that they possess the total set of variation presumably partitioned during later dispersal, represent such a true ancestor (generating an 'Out of France' rather than an 'Out of Africa' hypothesis). More exotic collecting locations, such as Africa and Asia, clearly beckon. More precise studies that provide a deeper analysis of individual nucleotide variation at several genes are required for this hypothesis to be confirmed. If the selection–migration explanation is correct, the ecology of the closely related *C. remanei* must be different from *C. elegans* (beyond the obvious difference in mating system), because it has much more typical levels of molecular variation than *C. elegans*.

These new studies of variation within individual populations of *C. elegans* demonstrate that variation can accumulate within local populations. The unanswered question, then, is where does that variation go as our focus moves to a more global scale? Why is there such limited evidence for local adaptation? Some natural isolates are clearly more 'natural' (and derived) than others. For example, the CB4856 strain from Hawaii differs from the standard N2 strain at approximately one SNP per 1000 base pairs. The key developments heralded by these new studies are a careful attention to sampling techniques and genetic analyses, and these new collections should rapidly replace the older strains that were isolated and documented much more haphazardly. We have little information on the natural ecology of *C. elegans*, but we are beginning to establish the genetic parameters within which these natural populations must operate.

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