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### The Genomic Basis of Nematode Parasitism

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**The Genomic Basis of Nematode Parasitism**

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**Key words.** Nematode, Parasite, Genomics, Evolution

For Peer Review

**Abstract**

Nematodes are highly abundant animals, and many species have a parasitic lifestyle. Nematode parasites are important pathogens of humans and other animals, and there is considerable interest in understanding their molecular and genomic adaptations to nematode parasitism. This has been approached in three main ways: comparing the genomes of closely related parasitic and free-living taxa, comparing the gene expression of parasitic and free-living life-cycle stages of parasitic nematode species, and analysing the molecules that parasitic nematodes excrete and secrete. To date these studies show that many species of parasitic nematodes have genomes that have large gene families coding for proteases / peptidases, protease inhibitors, SCP/TAPS proteins and acetylcholinesterases, and in many cases there is evidence that these appear to be used by parasitic stages inside hosts, and are often secreted. Many parasitic nematodes have taxa-specific gene families that also appeared to be involved in parasitism, emphasising that there is still much to be discovered about what it takes to be a parasitic nematode.

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27 **There are many nematode parasites**

28 Nematodes are the most abundant and species extant group of metazoans. Memorably,  
29 some 100 years ago Nathan Cobb said of nematodes: "*In short, if all the matter in the*  
30 *universe except the nematodes were swept away, our world would still be dimly*  
31 *recognizable ... we should find its mountains, hills, vales, rivers, lakes, and oceans*  
32 *represented by a film of nematodes. The location of towns would be decipherable, since*  
33 *for ... human beings there would be corresponding massing of certain nematodes. Trees*  
34 *would still stand in ghostly rows representing our streets and highways. The location of*  
35 *various plants and animals would still be decipherable...*" [1]. He made the point well, that  
36 nematodes are ubiquitous, if rather rarely seen. As Cobb also makes plain, they are also  
37 very common parasites, infecting all manner of multicellular animals and plants, in all  
38 terrestrial and aquatic environments, such that being parasitized by nematodes is a normal  
39 feature of life.

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41 Parasitic nematodes are diverse in their biology and life histories, so it can be difficult to  
42 make generalisations. However, by way of introduction, let us consider the most common  
43 nematode parasite of humans, *Ascaris lumbricoides*. Adult male and female worms  
44 (females are about 30 cm long, 5 mm in diameter; males are a little smaller) live in the host  
45 gut where they reproduce. Females lay eggs – some 250,000 per day – and these pass  
46 out of the host in its faeces. *Ascaris* eggs have a resistant egg shell and so the eggs  
47 persist in the environment for considerable periods of time. Hosts become infected when  
48 they accidentally ingest eggs. Once inside the host gut the eggs hatch to release a larva;  
49 this leaves the gut and migrates around the host body before returning to the gut where  
50 the worms then mature as adults, reproduce, and so the cycle continues. Other species of  
51 nematodes that parasitize vertebrates can live in other within-host sites, including blood  
52 vessels, the lymphatic system, and within the tissues. Parasitic nematodes have a myriad  
53 of different life cycles; for example, where larvae (rather than eggs) infect hosts; where  
54 worms are transmitted among hosts by arthropod vectors (in which case the parasite then  
55 lives in two different host species during its life), and where worms are transmitted when a  
56 host predate upon an infected host. Nematodes parasitize vertebrates, invertebrates and  
57 plants, though studies are biased towards those that parasite vertebrates – a bias that will  
58 persist in this article.

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60 Particular challenges for parasitic nematodes, to which they are adapted, are surviving  
61 within the host and transmitting among hosts. For parasites of vertebrates an important

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2 62 challenge is surviving the host anti-parasite immune response. There are two general  
3 63 strategies that parasitic nematodes use. The first is to evade the host immune response  
4 64 either by using a molecular disguise, by protecting themselves from host immune system  
5 65 effector molecules, or by living within certain within-host niches that are less  
6 66 immunologically exposed. The second, not mutually exclusive approach, is  
7 67 immunomodulation of the host, which appears to be very widespread among nematodes  
8 68 [2]. To immunomodulate their hosts nematodes release molecules into the host, and these  
9 69 interact with the host immune system to alter the host's immune response to the parasite's  
10 70 advantage. Though these immunomodulation phenomena are now well known, the  
11 71 detailed molecular mechanisms underlying these processes are currently largely unknown.  
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20 73 Parasitic nematodes cause immense harm to humans and other animals. More than 1.5  
21 74 billion people are infected with gastrointestinal nematode parasites, with this concentrated  
22 75 in the young, poor of the developing world [3, 4], and as such the World Health  
23 76 Organization recognises these infections as a neglected tropical disease [5]. The WHO  
24 77 estimates that in 2012, worldwide intestinal nematode infection caused a disease burden,  
25 78 measured by the Years Lost due to Disability (YLD), of 5 million YLD. This loss is greater  
26 79 than for other infectious diseases – 4 million for malaria, 4.5 million for HIV/AIDS [6].  
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32 80  
33 81 Nematode parasitism of agricultural animals is also very common and its control is  
34 82 necessary to maintain productivity and profitability [7, 8]. The production losses caused by  
35 83 parasitic nematode infection translates into economic costs: in the UK the estimated  
36 84 annual cost of nematode infection of sheep is €99 million. Across the EU the annual sales  
37 85 of anthelmintic drugs to treat nematode infections total approximately €400 million [8], but  
38 86 it is likely that this is actually only a small fraction of the true costs [9].  
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#### 44 87 45 88 **Nematodes are diverse**

46 89 Nematodes have a conservative morphology making traditional approaches to their  
47 90 taxonomy frustratingly hard, even for experts. Perhaps perversely, the nematodes are  
48 91 actually a highly diverse group of organisms. In molecular phylogenetic analyses  
49 92 nematodes often have considerably extended phylogenetic branches compared with other  
50 93 taxa, pointing to nematodes' elevated molecular evolutionary rates [10, 11]. One  
51 94 consequence of this is that many nematode species (and other taxonomic groupings) have  
52 95 genes and gene families that are specific to them [12].  
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2 97 This diversity is also seen in nematode genomes. *C. elegans* was the first nematode  
3 98 whose genome was sequenced, revealing a 100 Mb genome containing about 20,000  
4 99 genes. Since then the genomes of other nematodes have also be sequenced, particularly  
5 100 those of parasitic species. There are currently about 25 nematode genome sequences  
6 101 published, with about 100 projects on-going [13]. This work has already revealed  
7 102 substantial diversity in the size and content of nematode genomes. For example,  
8 103 sequenced nematode genomes now range from *c.* 20 Mb in *Pratylenchus coffeae* (a pest  
9 104 of bananas and other crops) coding for about 7,000 genes, to 370 Mb in *Haemonchus*  
10 105 *contortus* (a gastrointestinal parasite of sheep) coding for *c.* 20,000 genes [14, 15]. This  
11 106 variation in genome size is due to changes in gene number, as well as changes in the size  
12 107 and number of introns, and in the extent of non-coding, intervening sequence, including  
13 108 repetitive sequence [15–18]. It is also interesting to note that even within the  
14 109 *Caenorhabditis* genus that there are substantial differences in genome size and gene  
15 110 number. For example, genome size differs more than two-fold ranging from 79 Mb in *C.*  
16 111 *tropicalis* to 190 Mb in *C. brenneri*, while estimates of gene number range from the low of  
17 112 *C. elegans* to *c.* 35,000 in *C. sinica*. Despite these substantial differences among  
18 113 nematode species, signals of the conservation of gene order across large nematode  
19 114 distances can still be seen [15, 17, 19–21].  
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33 116 Phylogenetic analysis of nematodes has shown that they have independently evolved  
34 117 parasitism on up to 18 different occasions [22, 23]. Consequently, many parasitic  
35 118 nematodes have close relatives that have a free-living lifestyle. Species that parasitize  
36 119 different hosts (vertebrates, invertebrates, plants) are also often in the same nematode  
37 120 clades, perhaps suggesting that there is some deep conservation of adaptations to a  
38 121 parasitic lifestyle independent of the type of host being parasitized.  
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### 45 123 **Approaches to discovering the genetic and genomic basis of parasitism in** 46 124 **nematodes**

47 125 Parasitism is biologically fascinating, and so there is very considerable interest in  
48 126 understanding the adaptations that underlie the parasitic lifestyle. This basic biological  
49 127 interest is, of course, supplemented by a desire to understand the biology of these  
50 128 parasites so as to find ways to control them and the harm that they cause.  
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57 130 Prior to the advent of genomics a whole series of physiological and molecular studies were  
58 131 aimed at investigating aspects of parasitic nematodes' biology which, *a priori*, were likely  
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2 132 to be different in parasitic nematodes, compared with free-living species. So, for example,  
3 133 the metabolism of many nematode parasites of the vertebrate gut was investigated, given  
4 134 the likely special gaseous, pH *etc.* conditions in this environment. Similarly, because  
5 135 parasitic nematodes have to survive the host immune response there was considerable  
6 136 interest directed to understanding the structure and composition of parasitic nematodes'  
7 137 surface cuticle and its interaction with the host immune response.  
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13 139 In pursuing the aim of understanding the genetic basis of nematode parasitism there is an  
14 140 underlying rationale that all such studies use, and it is useful to make this rationale explicit.  
15 141 It is this: parasitic nematodes have evolved from free-living ancestors and as this has  
16 142 happened parasites will have adapted existing traits of their free-living nematode ancestor,  
17 143 and evolved new traits, which together underlie the parasitic lifestyle. Therefore,  
18 144 comparing free-living nematodes with parasitic nematodes can be used to uncover the  
19 145 molecular basis of nematode parasitism. This is the first type of genomic study used to  
20 146 understand nematode parasites. A second approach, but one using the same fundamental  
21 147 rationale, is to compare, within a species, parasitic life cycle stages with free-living life  
22 148 cycle stages. Finally, the third approach that is used seeks to discover which molecules  
23 149 parasitic stages likely excrete / secrete (*i.e.* ES material), with the rationale that many of  
24 150 these molecules will interact with the host in prosecuting a parasitic lifestyle.  
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### 34 152 **1. Comparing the genomes of parasitic and free-living nematodes**

35 153 This is potentially an enormously powerful approach to understand the genomic basis of  
36 154 nematode parasitism, but care must be taken in making the correct comparisons given the  
37 155 multiple, independent origins of nematode parasitism. Specifically, nematodes occur in five  
38 156 phylogenetic clades [22], with many clades containing both parasitic and free-living taxa.  
39 157 The most appropriate and powerful phylogenomic comparisons are those that compare  
40 158 taxa within the clades, rather than between clades. This is because parasitic vs. free-living  
41 159 comparisons across different clades confounds differences in lifestyles with the different  
42 160 evolutionary history of those clades. In contrast, comparisons between taxa with different  
43 161 lifestyles within the same clade can reasonably be used to infer the genomic bases of  
44 162 those differences in lifestyle. Given the very extensive genomic diversity among the  
45 163 nematodes, it is arguable that we currently have too few nematode genomes to make  
46 164 strong inferences about common genomic themes underlying parasitism across different  
47 165 nematode clades [13, 24]. Instead, more phylogenetically local, focused comparisons are  
48 166 probably more appropriate.  
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3 168 Because *C. elegans* was the first nematode genome to be sequenced, by necessity many  
4 169 studies of the genomes of parasitic nematodes have only been able to use *C. elegans*  
5 170 available as a comparator species. However, important parasitic species are in the same  
6 171 clade – for example, the hookworms *Necator* spp. and *Ancylostoma* spp., parasites of  
7 172 livestock such as *Haemonchus* spp., together with common laboratory models such as  
8 173 *Heligmosomoides polygyrus* and *Nippostrongylus brasiliensis* [22].  
9 174

10 175 One particularly useful genomic comparison between parasitic and free-living species  
11 176 involves six species within one sub-clade of nematodes. Specifically, this compared four  
12 177 obligate con-generic parasitic species (*Strongyloides* spp.), one facultative parasitic  
13 178 species (*Parastrongyloides trichosuri*), and one free-living species (*Rhabditophanes* sp.)  
14 179 all of whom are closely phylogenetically related (**Figure 1**). Comparison of these species'  
15 180 genomes was used to infer where genes and gene families arose, and where genes and  
16 181 gene families were lost, during the evolutionary history of the species and, crucially, as  
17 182 parasitism evolved (**Figure 1**). This analysis identified over 1,000 gene families that were  
18 183 evolutionarily acquired as the parasitic genera *Parastrongyloides* and *Strongyloides*  
19 184 evolved. Of these gene families, the two largest code for astacin-like zinc-  
20 185 metallopeptidases and SCP/TAPS proteins (known too by many other names, including  
21 186 CAP-domain, ASP and VAL proteins [25]). Specifically, the parasitic species *S. ratti* and *S.*  
22 187 *stercoralis* have 184 and 237 astacin-like metallopeptidase coding genes, compared with  
23 188 36 in the free-living relative *Rhabditophanes* (*C. elegans* has 40). For SCP/TAPS proteins,  
24 189 there were 89 and 113 coding genes in *S. ratti* and *S. stercoralis*, respectively, compared  
25 190 with 12 in *Rhabditophanes* (*C. elegans* has 36) [18].  
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27 192 The observed comparative expansion of astacin-like metallopeptidase coding genes in  
28 193 these parasitic taxa is consistent with similarly large gene families coding for peptidases  
29 194 and proteases in other parasitic nematode species [12]. For example, the *Ascaris suum*  
30 195 genome has 456 peptidase coding genes, with those coding for metallopeptidases and  
31 196 serine proteases predominating. The *Toxocara canis* genome has many similar genes too  
32 197 – 165, 107 and 60 (total 332) coding for metallo- cysteine and serine peptidases,  
33 198 respectively, together representing 89 % of all the predicated peptidase coding genes in  
34 199 this species [26]. In the whipworm *Trichuris suis* there are large numbers of genes coding  
35 200 for two classes of peptidases (116 for class S1 and 42 for class S8) [27]; *Dictyocaulus*  
36 201 *viviparus* has 478 protease coding genes [28]. Together, these results begin to suggest a

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2 202 common theme: that genomes of a range of parasitic nematodes have very many genes  
3 203 coding for proteases or peptidases [24], though the specific class of proteases / peptidase  
4 204 coded for appears to not be particularly consistent among different taxa.  
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8 206 The possible role for such an array of proteases and peptidases in nematode parasites is  
9 207 not known, but there are two main ideas for the role that they might play. Firstly, they might  
10 208 be used by the parasite to digest components of the host, at least in part to acquire food.  
11 209 *Strongyloides* spp., as many other parasitic nematode species, undergoes a within-host  
12 210 migration before finally settling in the gut. This migration requires the breakdown of host  
13 211 tissue, which presumably these parasite-produced enzymes achieve. Furthermore,  
14 212 *Strongyloides* actually lives within and continuously burrows through the mucosa of the  
15 213 host's small intestine [29]. Here the parasite is presumably digesting host tissue, which is  
16 214 then used as a food source by the parasite. In *Strongyloides* it is likely that the  
17 215 metallopeptidases are secreted by the parasite to achieve this. Other species of parasitic  
18 216 nematodes feed on the host in other ways, and the ability to digest host proteins would  
19 217 therefore seem to be a key component of living a parasitic lifestyle. The second potential  
20 218 role of proteases in the parasitic lifestyle concerns immunomodulation of their hosts. Here  
21 219 the idea is that these proteases act against, and disable, protein components of the host  
22 220 immune response, which thereby facilitates the parasites' survival.  
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35 222 Turning to the second group of genes that are comparatively expanded in *Strongyloides*,  
36 223 compared with free-living species, the SCP/TAPS proteins. The expansion of this gene  
37 224 family in *Strongyloides* also chimes with analyses of genomes of other species [12]. For  
38 225 example, the hookworms *Ancylostoma ceylanicum* and *Necator americanus* have 432 and  
39 226 137 of these genes [30, 31], and *Haemonchus contortus* 161, compared with 36 in the  
40 227 free-living species *C. elegans* (and as a further comparison, there are 33 in *Pristionchus*  
41 228 *pacificus*, which lives in close association with beetles, but does not appear to be a  
42 229 parasite [32]). This gene family is also reported to be expanded in another clade V  
43 230 nematode, *Dictyocaulus viviparus* [28].  
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51 232 There has been substantial interest in the SCP/TAPS proteins in parasitic nematodes, in  
52 233 large part because these molecules appear to be abundant in nematode parasites [25],  
53 234 with some of these proteins being immunodominant. Despite this notoriety, what these  
54 235 molecules actually do in parasitic nematodes remains far from clear. *In vitro* evidence is  
55 236 consistent with some of these molecules interacting with components of the host immune  
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2 237 responses [33]. In *Heligmosomoides polygyrus* and *Ancylostoma caninum* SCP/TAPS  
3 238 molecules are on (and closely below) the parasite surface, as well as associated with the  
4 239 parasite's gut and oesophagus. This is consistent with these molecules having a role in  
5 240 immunomodulating the host, but also consistent with interacting with the host more widely  
6 241 [25, 34]. More generally, related molecules occur in a wide variety of non-parasitic species,  
7 242 perhaps suggesting that the conserved features of these proteins are simply domains that  
8 243 can be usefully deployed in many settings [25].  
9 244

10 245 Within the *Strongyloides* clade of nematodes, other gene families that expanded  
11 246 coincident with the evolution of parasitism include acetylcholinesterase-coding genes (33  
12 247 and 34 in *S. ratti* and *S. stercoralis*, respectively, compared with 3 in *Rhabditophanes*; *C.*  
13 248 *elegans* has 4), receptor-type protein tyrosine phosphatase-coding genes (83 and 75 in *S.*  
14 249 *ratti* and *S. stercoralis*, respectively, compared with 21 in *Rhabditophanes*; *C. elegans* has  
15 250 59). The role of parasitic nematode-produced acetylcholinesterases in the parasitic lifestyle  
16 251 is also not fully understood. In some species of gastrointestinal parasitic nematodes these  
17 252 molecules are secreted into the host gut where they have been thought to play a role in  
18 253 modulating the activity of the gut – including muscular contraction of the gut, as well as  
19 254 secretion of mucus and other fluid – with this facilitating parasite survival [35]. However,  
20 255 more recently parasite acetylcholinesterases have also been found to have an  
21 256 immunoregulatory role [36]. Careful assessment of this large family of genes in  
22 257 *Strongyloides* very strongly suggests that, when translated, many of these gene products  
23 258 will be enzymatically inactive [37]. One possibility, therefore, is that this comparatively  
24 259 expanded gene family is a functionless family, though this then begs the question of why  
25 260 such a large family of putatively non-functional proteins became expanded and are  
26 261 maintained in a genome, and why they appear to be secreted by the parasitic stages of  
27 262 the life cycle. An alternative explanation is that these genes are coding for proteins with  
28 263 other functionalities that are completely unrelated to the acetylcholinesterase-like  
29 264 enzymatic function.  
30 265

31 266 Importantly, in many of these genomic comparisons between parasitic and free-living  
32 267 species, gene families whose products are (i) hitherto unknown and (ii) unique to the taxa  
33 268 in which they are described have been found [12]. Given the diversity among nematode  
34 269 taxa, the existence of taxa-specific gene families should be expected. Indeed, such taxa-  
35 270 specific gene families should be as likely to occur among free-living species, as well as  
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2 271 parasitic. Because of the taxa-specific nature of these gene families, their possible role in  
3 272 parasitism is unclear, though this is clearly a research challenge for the future.  
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## 6 274 **2. Comparing parasitic and free-living stages**

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8 275 This approach exploits the fact that many species of parasitic nematode have life cycles  
9 276 where some stages are parasitic and some are free-living (with these used for  
10 277 transmission among hosts). Comparing gene expression in parasitic and free-living life  
11 278 cycle stages might therefore identify the genes and proteins used specifically (or more) by  
12 279 the parasitic stages, which can then be used to infer what structures, metabolism,  
13 280 molecular processes *etc.* underlie the parasitic lifestyle of the species concerned.  
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20 282 Interpreting results from such comparisons can be problematic, for two related reasons.  
21 283 Firstly, these comparisons involve both different life cycle stages (for example larvae and  
22 284 adults) and different lifestyles (free-living vs. parasitic). Put formally, such comparisons  
23 285 therefore confound life cycle stage and lifestyle. This is a real problem because there can  
24 286 be considerable differences in the biology of different nematode life cycle stages, even  
25 287 when they are all living in the same environment. This can be seen using an example from  
26 288 the life cycle of the free-living nematode *C. elegans*. It has about 170 genes that code for  
27 289 collagen proteins, which are the principal component of its cuticle (as for all nematodes).  
28 290 Nematodes, including *C. elegans*, moult through four larval stages, before moulting into  
29 291 adult stages, and at each moult a new cuticle is formed. In *C. elegans* different groups of  
30 292 collagen coding genes are used by each life cycle stage. Therefore transcriptomic  
31 293 comparison of different *C. elegans* life cycle stages would reveal life cycle stage-specific  
32 294 differences in the transcription of collagen coding genes. If these different life cycle stages  
33 295 had different lifestyles (such as free-living and parasitic) then we might wrongly infer that  
34 296 collagen molecules were an adaptation to the parasitic lifestyle. A second, related problem  
35 297 of comparing transcriptomes or proteomes between different nematode life cycle stages is  
36 298 that the results obtained depend on what is compared with what.  
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51 300 Notwithstanding these caveats, comparative transcriptomic methods have been widely  
52 301 used, mainly focused on two within-host parasitic stages: (i) larval stages that infect hosts,  
53 302 and (ii) adult stages living and reproducing within hosts. The results are difficult to  
54 303 synthesise and summarise because of the diversity of comparisons made among many  
55 304 different parasitic taxa. In studies of infective larvae newly arrived within a host, increased  
56 305 transcription of genes whose products are involved in growth, metabolism, sensory  
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2 306 processes *etc.* are observed (for example in *D. viviparous* and *H. contortus* [15, 28]),  
3 307 consistent with the parasites resuming growth and development once entry into a host has  
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5 308 been achieved. The expression of genes coding for proteases, and protease inhibitors, is  
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7 309 also often seen (for example in *Ancylostoma* spp. and *Ascaris suum* [21, 31, 38])  
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9 310 presumably reflecting the need of migratory larvae stages to digest host tissue as they  
10 311 migrate.

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13 313 For parasitic adult stages, there is also a comparative increase in the expression of genes  
14 314 coding for a range of enzymes including proteases, peptidases, hydrolases, catalases (for  
15 315 example in *N. americanus*, *H. contortus*, *Toxocara canis* and *Ascaris suum* [15, 21, 26,  
16 316 30]), and protease inhibitors. Also, consistent with adult stages growing and reproducing,  
17 317 there is a comparative increase in transcription of genes whose products are involved in  
18 318 DNA replication, cuticle formation, spermatogenesis.

19 319  
20 320 A more nuanced analysis of the hookworm *Ancylostoma ceylanicum* compared parasitic  
21 321 stages at different times after infection, showing that in worms' first few days within a host  
22 322 SCP/TAPS proteins had comparatively enhanced transcription, but in more established  
23 323 worms there was a comparative increase in the transcription of genes whose products are  
24 324 likely involved in growth (for example genes coding for cuticle components, and proteins  
25 325 that are able to bind cytoskeleton proteins [31]). Later still in infection the transcription  
26 326 profile alters towards genes coding for protein tyrosine phosphatases, serine / threonine  
27 327 kinases, and C-lectins. These observations make the important, more general point that  
28 328 parasitic nematodes live a dynamic life where aspects of their biology change as the  
29 329 within-host environment alters. For example, hosts have changing physiological states  
30 330 (*e.g.* reproductive state, nutritional state, seasonal changes *etc.*) as well as different  
31 331 infections and co-infections [39] with consequent effects on the host immune response, all  
32 332 of which changes the within-host environment to which parasitic nematodes are exposed.

33 333  
34 334 For *Strongyloides* nematodes, an unusual feature of their life cycle largely overcomes the  
35 335 problem of confounding lifestyle with life cycle stage. This is because the *Strongyloides* life  
36 336 cycle has two adult generations – one parasitic (which is female only) and one free-living  
37 337 (which is dioecious). In this case, comparison of parasitic adult female worms with free-  
38 338 living adult female worms compares lifestyle, without life cycle stage being a confounding  
39 339 factor. Comparison of the transcriptome of these free-living and parasitic adults of *S. ratti*  
40 340 showed that the parasitic females had significantly enhanced transcription of astacin-

1  
2 341 metallopeptidase and SCP/TAPS coding genes – the same gene families that are  
3 342 comparatively enlarged in these genomes [18]. In addition to this, genes coding for  
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5 343 transthyretin-like proteins, prolyl endopeptidases, aspartic peptidases,  
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7 344 acetylcholinesterases, trypsin inhibitors also had comparatively greater expression in  
8  
9 345 parasitic females [18]. Importantly, up to a third of all genes differentially expressed  
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11 346 between these stages were hitherto unknown, hypothetical protein-coding genes, including  
12  
13 347 some gene families that appear to be unique to these parasitic taxa [18], with similar  
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15 348 phenomena reported in other species too [40].  
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17 349  
18 350 For some larger parasitic adult worms gene transcription in different regions of the worms'  
19 351 bodies have been analysed [41]. For example, the whipworms *Trichuris* have a structurally  
20 352 modified anterior end (called the stichosome), and this anterior end lies embedded within  
21 353 the hosts' mucosa, while the worms' posterior end lies free in the host gut lumen into  
22 354 which worm eggs are then easily liberated. Transcriptional analysis of the stichosome  
23 355 (compared with the rest of the adult worm) of *T. suis* shows comparatively greater  
24 356 expression of many genes coding for peptidases and for porins (along with many other  
25 357 genes), consistent with the idea that the stichosome function is to allow the worm to  
26 358 burrow into host tissue [27, 42]. The transcriptional profile of the gut of two parasitic  
27 359 nematodes (*H. contortus* and *T. canis*, [15, 26]) has also shown that genes coding for a  
28 360 range of protease / peptidases (and protease and peptidase inhibitors), and products  
29 361 involved in binding with and transporting a range of molecules, are comparatively  
30 362 upregulated, consistent with the *a priori* view of the function of the worm's gut.  
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41 364 In summary, studies that have sought to discover the genes specifically used by within-  
42 365 host parasitic stages have shown that many different gene families are used. Often these  
43 366 genes belong to families that appear to be comparatively expanded in parasitic species,  
44 367 strengthening the inference that these genes have a special role in parasitism. Beyond  
45 368 this, many of the other genes specifically expressed by these adult stages are consistent  
46 369 with growth and reproduction, which is clearly the principal biological function of within-  
47 370 host adult parasitic stages.  
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### 53 372 **3. Secreted molecules**

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55 373 Identifying the molecules that nematode parasites secrete into their hosts aims to  
56 374 understand the interactive interface between parasites and their hosts. Two approaches  
57 375 are used: proteomic analysis of excretory / secretory (ES) molecules, and genomic  
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2 376 analysis of genes whose products are predicted to be secreted.

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5 378 There has been relatively limited proteomic analysis of parasitic nematodes. Of particular  
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7 379 note are the analysis of the ES of *Heligmosomoides polygyrus*, showing that this  
8  
9 380 contained more than 400 ES-specific proteins. SCP-TAPS proteins dominated the ES, but  
10 381 they also contained proteases, lysozymes, apyrases and acetylcholinesterases [25]. In the  
11 382 hookworm *Ancylostoma caninum* its ES also contained similar groups of proteins, but  
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13 383 lectins and galectins too [40]. Given that different species of parasitic nematodes have  
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15 384 different within-host niches, and so different biology, the molecules they secrete to interact  
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17 385 with their host are likely to vary in respect of their different biology. For *Haemonchus*  
18 386 *contortus*, proteomic analyses of its ES has focused on those proteins that are  
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20 387 immunologically recognized by hosts [43]. A wide variety of molecules were identified  
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22 388 including, once again, proteases. However, notably, the most immunogenic molecules in  
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24 389 these ES was a transthyretin-like protein [43]. In *S. ratti* the secreted proteome of parasitic  
25 390 and free-living females, and infective larvae was compared, finding a range of proteins  
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27 391 specifically secreted by the parasitic stage, including proteases, prolyl endopeptidases and  
28 392 acetylcholinesterases [44].

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32 394 Proteomic analyses are the most direct way of characterising parasites' ES. However,  
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34 395 many studies have used a transcriptomic approach where ES molecules are  
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36 396 computationally predicted based on the presence of signal peptides and the absence of  
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38 397 trans-membrane domains – a so-called secretome – though, of course, this approach does  
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40 398 not only identify those proteins specifically secreted outside of the worm. While this is a  
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42 399 widespread approach, there is a worrying empirical discordance between protein and  
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44 400 transcript abundance, probably because of post-translational modifications which  
45 401 decouples the abundance of mRNA transcripts from the quantity of protein present [45–  
46 402 47].

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48 404 Many of the results from analyses of predicted secretome overlap with results obtained  
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50 405 from the two other approaches (above) used to investigate nematode parasitism. The  
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52 406 predicted secretome can be large – in *Necator americanus* it is a third of the entire  
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54 407 proteome. In this species, genes whose expression was comparatively greater in parasitic  
55 408 stages are more likely to be predicted secretory molecules (*N. americanus*, *S. ratti*) [18,  
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57 409 30].

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2 411 In many species, proteases and peptidases are predicted to be secreted (*Ascaris suum*,  
3 412 *Toxocara canis*, *Trichuris suis*, *S. ratti* [18, 21, 26, 27]); in *N. americanus* over half (325 of  
4 413 592) of all proteases fall into this category, and 19 % of the 478 of *Dictyocaulus viviparus*  
5 414 [28]. Some SCP/TAPS proteins are also predicted to be secreted (in *Ascaris suum*,  
6 415 *Toxocara canis*, *S. ratti*, *D. viviparus*). But, species also differ in their predicted secretome.  
7 416 For example in *Ascaris suum*, o-linked glycosylated proteins are the single largest group of  
8 417 predicted secreted proteins, while other species have a diversity of molecules often  
9 418 implicated in immunomodulatory roles [21].  
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### 17 420 **The genomic basis of nematode parasitism and prospects for the future**

18 421 While impressive advances have been made in interrogating nematode genomes these  
19 422 studies are still essentially at an early stage, especially given the diversity that exists  
20 423 among the nematodes. Notwithstanding this, it appears that the genomes of many  
21 424 parasitic nematodes are abundantly resourced with some particular gene families – those  
22 425 coding for proteases / peptidases, protease inhibitors, SCP/TAPS proteins,  
23 426 acetylcholinesterases *etc.* – and in many cases these genes appear to be used especially  
24 427 during the within-host parasitic stages, and are often secreted [18, 44]. The apparent  
25 428 preponderance of proteases / peptidases and protease inhibitors makes the, perhaps  
26 429 obvious, point that parasitic nematodes make their living by managing and manipulating  
27 430 host proteins and that, similarly, hosts seek to interact with parasite proteins (which  
28 431 parasites, in turn, aim to resist). The apparent widespread occurrence of SCP/TAPS  
29 432 proteins in parasitic nematodes is fascinating, but it remains frustrating that we have such  
30 433 a limited understanding of what these molecules might do.  
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42 435 One consistent, if somewhat opaque, finding in many of these studies is that there are  
43 436 often taxa-specific genes and gene families, and that these often have many of the  
44 437 hallmarks of being involved in the parasitic lifestyle. Discovering what the products of  
45 438 these genes do is clearly an important task to be able to fully understand the biology of  
46 439 nematode parasitism. This also makes the more general point that different groups of  
47 440 nematodes' genomes are specialised in different ways for a parasitic lifestyle, and in the  
48 441 molecules they use and secrete as they interact with the host. While this diversity of  
49 442 function might be daunting, it might also give very good purchase on separating out  
50 443 nematode-wide, from taxa-specific, aspects of nematode parasitism.  
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2 445 Over the next few years it can be envisaged that further great strides will be made in  
3 446 interrogating the genomes of parasitic nematodes. However, beyond genomic analyses  
4 447 functional manipulations of genomes will be needed to rigorously test hypotheses  
5 448 concerning the function of particular genes and their products. Despite the enormous  
6 449 success of transgenesis, RNAi analysis and genome editing *etc.* in *C. elegans*, these  
7 450 methods have proved very much harder to establish with parasitic species. For example, it  
8 451 appears that parasitic nematodes are generally refractory to RNAi [48], whereas *C.*  
9 452 *elegans* is, by lucky chance, particularly susceptible (and indeed more susceptible than  
10 453 most other *Caenorhabditis* spp. [49]). Clearly, for parasitic nematodes the use of such  
11 454 approaches is considerably more tricky because of the need for these parasites to be  
12 455 maintained in (usually vertebrate) hosts. However, progress is being made, particularly  
13 456 with *Strongyloides* spp., where transgenesis is possible, and where the first evidence for  
14 457 the use of CRISPR has now been obtained [50]. Using these and other techniques we will  
15 458 eventually reveal how nematodes live their parasitic lives, and so we will answer a  
16 459 fundamentally fascinating question, but also be able to consider how to manipulate and  
17 460 control these organisms so as to alleviate human and animal suffering.  
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28 461

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30 463

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32 465 Vicky Hunt for useful discussions, and the Wellcome Trust for funding support.  
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39 467 **Figure Legend**

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41 469 **Figure 1. The phylogeny of *Strongyloides* and its relatives and the evolution of**  
42 **parasitism.** A phylogeny of four species of *Strongyloides*, *Parastrongyloides trichosuri* and  
43 *Rhabditophanes* sp. *Rhabditophanes* is a free-living species. *Parastrongyloides* can have  
44 multiple free-living adult generations, but can also be parasitic, making it a facultative  
45 parasite. *Strongyloides* is an obligate parasitic species because, even though it has a free-  
46 living adult generation (as does *Parastrongyloides*), *Strongyloides*' life cycle requires a  
47 parasitic adult generation every generation. Where parasitism and obligate parasitism are  
48 inferred to arise is shown. The boxes show, in descending vertical order, the number of (i)  
49 gene families originating on each branch (+, in blue), (ii) gene families with at least one  
50 duplication event on each branch (+, in blue, in parentheses), and (iii) the number of gene  
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2 479 families with at least one loss on each branch (-, in red). The tree branch lengths do not  
3 480 show the relative distance among the taxa. Data from [18].  
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7 482 **References**

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2 6523 653 **Author Biography**4  
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7 655 Mark Viney studies the biology of nematodes, particularly parasitic species, seeking to  
8 656 understand how the environment controls their development, and how they are adapted to  
9 657 their parasitic lifestyle. (nematode.bio.bris.ac.uk)

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11 65812  
13 659 **Summary Key Points**14  
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17 661 1. Nematodes are ubiquitous and abundant animals and many species are parasites.  
18 662 2. Nematodes have evolved parasitism on multiple different occasions.  
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20 663 3. Phylogenetically appropriate comparisons of parasitic and free-living nematodes  
21 664 can reveal nematodes' genomic adaptations to parasitism.  
22  
23 665 4. Different parasitic nematodes have taxa-specific adaptations to parasitism, though  
24 666 the comparative expansion of genes and gene families coding for proteases and  
25 667 SCP/TAPS proteins appears to be a common theme among them.  
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27 668 5. Parasitic nematodes' secreted molecules are the key interface between host and  
28 669 parasite, and discovering these molecules will be instrumental in understanding  
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30 670 how nematodes are adapted to their parasitic lifestyle.  
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Figure 1

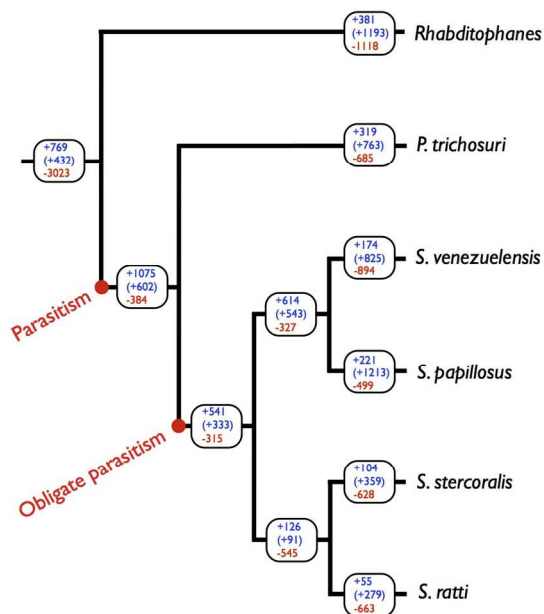


Figure 1. The phylogeny of Strongyloides and its relatives and the evolution of parasitism. A phylogeny of four species of Strongyloides, Parastrongyloides trichosuri and Rhabditophanes sp. Rhabditophanes is a free-living species. Parastrongyloides can have multiple free-living adult generations, but can also be parasitic, making it a facultative parasite. Strongyloides is an obligate parasitic species because, even though it has a free-living adult generation (as does Parastrongyloides), Strongyloides' life cycle requires a parasitic adult generation every generation. Where parasitism and obligate parasitism are inferred to arise is shown. The boxes show, in descending vertical order, the number of (i) gene families originating on each branch (+, in blue), (ii) gene families with at least one duplication event on each branch (+, in blue, in parentheses), and (iii) the number of gene families with at least one loss on each branch (-, in red). The tree branch lengths do not show the relative distance among the taxa. Data from [18].

297x209mm (150 x 150 DPI)